(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2005 (13.10.2005)

PCT

(10) International Publication Number
WO 2005/094782 A1

(51) International Patent Classification[7]: A61K 9/00, 9/14, 31/00, 9/127, A23L 1/29, 1/00, A23G 3/00, G01F 1/56

(21) International Application Number:
PCT/CA2004/001896

(22) International Filing Date: 29 October 2004 (29.10.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/558,906 1 April 2004 (01.04.2004) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 10/416,547 (CON)
Filed on 25 March 2003 (25.03.2003)

(71) Applicant *(for all designated States except US)*: VITAL-STATE US, INC. [US/US]; 1499 High Ridge Road, Boyton Beach, FL 33426 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: FARBER, Jonathan [CA/CA]; 8804 Ernest Savignac, Montreal, Québec H2M 2M3 (CA).

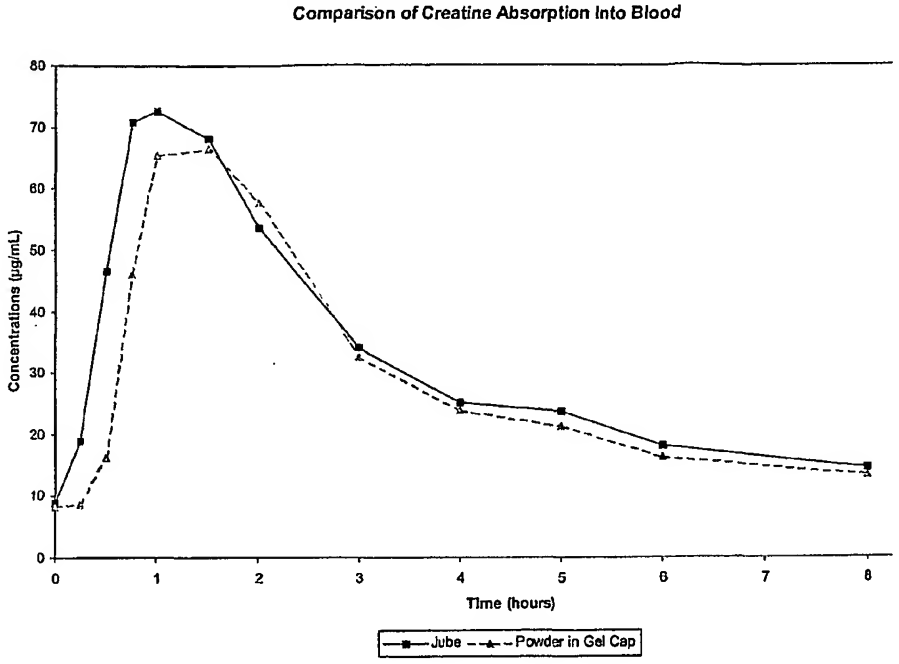
(74) Agent: MBM & CO.; P.O. Box 809, Station B, Ottawa, Ontario K1P 5G8 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

[Continued on next page]

(54) Title: DELIVERY SYSTEMS FOR ANTACIDS



(57) Abstract: Oral gel delivery systems for antacids are provided comprising an ingestible matrix within which one or more antacid is substancially uniformaly and completely dispersed. The delivery systems may optionally include one or more other functional ingredients, for example, functional ingredients that complement or enhance the function of antacids within the body.

WO 2005/094782 A1

European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *with international search report*

DELIVERY SYSTEMS FOR ANTACIDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application Serial No. 10/416,547, filed March 25, 2003, which is a national stage of PCT application PCT/CA03/00411, filed March 25, 2003. The aforesaid PCT application claims priority from U.S. Provisional Patent Application Serial No. 60/372,438, filed April 16, 2002. The contents of all of the aforementioned applications are hereby specifically incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention pertains to the field of oral delivery systems, in particular to a gel delivery system for antacids.

BACKGROUND OF THE INVENTION

Antacids are widely used in the treatment of gastrointestinal disorders. Their effectiveness in promoting the healing of gastric and duodenal ulcers has been well documented. The United States Pharmacopoeia defines an antacid in terms of its ability to neutralise acid. To be called an antacid, the lowest dose of the substance when added to 10 mL of 0.5 N HCl (5 mEq) must produce a pH of 3.5 or greater after 10 minutes of stirring. The clinical use of antacids is based on their ability to neutralise stomach acid and increase the pH of the gastric secretions. Increasing the gastric pH from 1.3 to 2.3 neutralises 90% of gastric acid and increasing the pH to 3.3 neutralises 99% of gastric acid. The proteolytic activity of pepsin is also inhibited when the pH of stomach contents is raised above 3.0. For optimal healing of peptic ulcers, most clinicians believe that gastric pH should be maintained at about 3.0 to 3.5. The therapeutic role of antacids, particularly in ulcer therapy, rather than a merely palliative role, has emphasised the importance of providing effective antacid products.

Most antacids are available in both liquid and solid dosage forms. The liquid antacids, as aqueous suspensions, are generally believed to be more effective than the same antacids in solid dosage forms and are more commonly prescribed in the hospital setting. The greater effectiveness of liquid antacids may be due in part to the large surface area available in liquid suspensions to react with gastric acid and partially due to the great amount of colloidal particles in aqueous suspension which can more easily reach the affected area where treatment is needed. Moreover, aqueous suspensions of undehydrated antacids are more reactive than dry or solid antacids.

While liquid antacids possess these advantages, the same require administration of relatively large volumes of liquid suspension. The ingestion of such large volumes is inconvenient, however, making the normal problem of assuring patient compliance outside the hospital environment even more difficult.

Pharmaceutical solid dosage forms are available that are designed to be chewed either to provide proper flavour or to increase the surface area of a particular drug to permit rapid activity in the digestive tract or circulatory systems. Substantial levels of antacid are needed in order to achieve the optimal buffering profile and the large amounts of metal salts in the solid dosage forms and can have both an unpleasant mouth feel and unpalatable taste due to the chalkiness, grittiness, dryness and astringent properties of these materials. Accordingly, the practical value of these materials is substantially diminished since patients finding them objectionable may fail to take them as prescribed.

Various chewable pharmaceutical solid dosage forms that could be adapted for antacid delivery have been described. For example, United Kingdom Patent Applications GB 2 195 892 and GB 2 195 891 describe lipid-containing moulded chewable tablets that include a lipid material, a dispersant, an emulsifier and a safe and effective amount of a pharmaceutically active material. The tablets of the lipid composition are described as exhibiting improved palatability, and effective dispersion in the mouth and stomach.

U.S. Patent No. 5,753,255 describes a chewable medicinal tablet, which contains about 30 to about 95% by weight of a capric triglyceride and a medicinally active

ingredient up to 60% by weight. If the medicinally active ingredient is less than about 30% by weight, then the composition also contains up to 10% by weight of glyceryl monostearate, a mixture of glyceryl monostearate and glyceryl monopalmitate, or a mixture of glyceryl monostearate and glyceryl distearate.

U.S. Patent No. 4,684,534 describes quick-liquefying, chewable tablets. The tablets have a harder outer shell, which inhibits penetration of liquid, and a softer interior which quickly liquefies when the tablet and shell are broken into pieces and contacted by the liquid. The excipient or base material of the tablet is made from carbohydrates held together with small quantities of a carbohydrate binder such as maltodextrin. The tablets are described as being able to contain active ingredients such as pharmaceuticals, breath sweeteners, vitamins and dietary supplements.

U.S. Patent No. 6,589,556 describes rapid melt semi-solid product formulations containing one or more certain lipid materials, emulsifiers and particulate materials for the delivery of pharmaceutical active materials.

U.S. Patent No 5,686,107 describes formulations of chewable pharmaceutical tablets for delivery of prescription pharmaceutical actives, non-prescription pharmaceutical actives, or over-the-counter actives, including an antacid and optionally an antigas compound, comprising as an excipient, an aggregate of coprocessed microcrystalline cellulose and a galaotomannan.

U.S. Patent No. 5,260,304 describes a pharmaceutical preparation binding with gastric acid comprising granules, possibly in tablet form. The granules contain at least one insoluble, complexed or slightly soluble active substance in powder form which can bind or neutralise acids and which does not react with the acid of the effervescent system, and an effervescent system consisting of at least one organic, edible acid and at least one alkali metal and/or alkaline earth metal carbonate and/or bicarbonate. The system contains a hydrocolloid selected from xanthan, maltodextrin, galactomannan and tragacanth.

U.S. Patent No. 6,589,551 describes a chewable oral unit dosage comprising a substrate defining a plurality of discrete reservoirs each containing a liquid fill with an active ingredient dissolved or dispersed therein for release in the mouth.

U.S. Patent No. 6,602,518 describes products with a chewable centre and a consumable powder containing a medicament, which may or may not be encapsulated, the powder being compressed around the centre. The medicament is described as being any one of a number of drugs, therapeutic compounds, vitamins, minerals or nutraceuticals.

U.S. Patent No. 6,692,771 describes emulsion compositions adsorbed onto solid particles which may be further formulated into solid dosage forms to improve the drug-load and the bioavailability of a wide range of drugs.

International Patent Application WO 98/20860 describes a chewable composition comprising sweetener, carageenan and water for delivery of a pharmacologically active material. The system may also include locust bean gum, starch, konjac or guar gum. At solids levels below 78%, the system is not shelf stable and requires the presence of a preservative. Pharmacologically active materials are described as including antacids, antihistamines, antipyretics, anti-inflammatories, antivirals, antibiotics, anti-tussives, expectorants and nutritional supplements.

Other chewable delivery systems have been described. Troches (or lozenges), for example, are a traditional drug dosage format that is based on gelatine and glycerine and used in preparing custom medications by hand for individual patients. Troches are made in small quantities from a base that typically comprises 70% glycerine, 10% gelatine and 20% water. The water is slowly driven off by heating the base and the final composition, which tends to absorb moisture from the air, is stored under refrigeration. The troche itself is made by re-melting the base and adding milligram quantities of an active ingredient. Troches are not stable and are intended to be consumed within thirty days. Typically, methyl paraben is included in the base material to prevent microbial spoilage.

U.S. Patent No. 4,882,154 describes a more shelf-stable gelatine-based chewable delivery system for pharmaceuticals, vitamins or minerals. This system, however, requires the use of pre-coated drugs, vitamins and minerals in order to preserve the stability of these compounds. International Patent Applications WO 03/026438, WO 03/026439 and WO 03/088755 describe gel-like delivery systems for creatine and other functional ingredients. The delivery systems described by these latter applications comprise as essential components a carbohydrate (such as a starch) and at least one hydrocolloid component (such as gelatine or a plant gum).

A number of different solid antacid formulations have been described that were designed to improve the mouth feel and palatability of antacid compounds. For example, U.S. Patent No. 6,645,535 describes a method of making antacid chewing gum products which involves coating chewing gum cores with a coating syrup made from a bulk sweetener and a neutralising antacid selected aluminium salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mixtures thereof.

U.S. Patent No. 5,762,962 describes tabletting compositions which use dihydroxy aluminium sodium carbonate (DASC) to provide an antacid that is both fast acting and long lasting. The compositions are described as good tasting with a palatable mouthfeel.

U.S. Patent No. 4,609,543 describes a soft homogeneous antacid tablet. The tablet contains solid antacid particles thoroughly coated with a mixture composed of a fatty material or oil, a surfactant, and a flavour. The fat or oil is present in an amount of from about 25% to about 45% of the mixture.

U.S. Patent No. 4,446,135 describes chewable calcium carbonate-containing antacid tablets. The tablets are described as having good mouthfeel properties due to the use of calcium carbonate of a particular particle size (5 to 50 microns in diameter), in combination with certain excipients.

U.S. Patent Nos. 4,327,076 and 4,327,077 describe a compressed chewable antacid tablet, which has good flexibility, is breakage resistant and disintegrates immediately

upon chewing. The tablet is formed of a recrystallized fatty material, such as chocolate, a bulking material and an active ingredient bound up in the particles of the recrystallized fatty material.

This background information is provided for the purpose of making known information believed by the applicant to be of possible relevance to the present invention. No admission is necessarily intended, nor should be construed, that any of the preceding information constitutes prior art against the present invention.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a delivery system for antacids. In accordance with an aspect of the present invention, there is provided an oral gel delivery system for antacids comprising one or more antacid An oral gel delivery system for antacids comprising one or more antacids substantially uniformly dispersed in a gel matrix, said delivery system having a final moisture content of between about 10% and about 40% by weight and a water activity of less than about 0.9, and said gel matrix comprising: (a) one or more hydrocolloids; (b) one or more sugars, sugar syrups, sugar alcohols, or a combination thereof; and (c) one or more polyhydric alcohols.

In accordance with another aspect of the present invention, there is provided an oral gel delivery system for antacids comprising one or more antacids substantially uniformly dispersed in a gel matrix, said delivery system having a final moisture content of between about 10% and about 30% by weight and a water activity of less than about 0.7, and said gel matrix comprising: (a) one or more hydrocolloids selected from the group of: modified starch, gelatine, gellan, pectin, cellulose and modified cellulose; (b) one or more sugar syrups selected from the group of: corn syrup, high fructose corn syrup, maltitol syrup and isomalt syrup, and (c) one or more polyhydric alcohols selected from the group of: glycerol and propylene glycol.

In accordance with another aspect, the oral gel delivery system of the present invention further comprises one or more other functional ingredients, wherein the

total amount of said one or more antacids and said one or more functional ingredients is less than or equal to 40% by weight of said delivery system.

In accordance with another aspect of the present invention, there is provided a use of a gel matrix comprising: (a) one or more hydrocolloids; (b) one or more sugars, sugar syrups, sugar alcohols, or a combination thereof, and (c) one or more polyhydric alcohols, in the preparation of an oral gel delivery system for antacids, wherein said delivery system comprises one or more antacids substantially uniformly dispersed in said gel matrix, and said delivery system has a final moisture content of between about 10% and about 40% by weight and a water activity of less than about 0.9.

In accordance with another aspect of the present invention, there is provided a process for preparing an oral gel delivery system for antacids, said process comprising the steps of: (i) preparing a blend of one or more hydrocolloids, one or more sugars, sugar syrups, sugar alcohols, or a combination thereof, and optionally water at a temperature of less than 100°C, wherein said hydrocolloid(s), said sugars, sugar syrups and/or sugar alcohols and said water are in a ratio that will provide a final moisture content to the delivery system of between about 10% and about 40% by weight; (ii) reducing the temperature of said blend to between about 50°C and about 80°C; (iii) dispersing one or more antacids in a solvent comprising one or more polyhydric alcohols at a temperature at or below about 70°C to provide a solvent mixture; (iv) combining said blend from step (ii) with said solvent mixture to provide a gel matrix, and (v) moulding said gel matrix to provide said oral gel delivery system.

In accordance with another aspect of the present invention, there is provided an oral gel delivery system for antacids prepared by the above-described process

In accordance with another aspect, there is provided a use of the oral gel delivery system of the invention to deliver an effective amount of one or more antacids to an animal in need thereof.

In accordance with another aspect, there is provided a kit for the delivery of antacids to an animal comprising one or more units of the oral gel delivery system of the invention and optionally instructions for use.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 demonstrates absorption of a functional ingredient into the blood following administration of a delivery system prepared with a gel matrix according to one embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. As used herein, percentage values (%) represent the weight percentages of the total weight of the delivery system.

The term "functional ingredient," as used herein, includes physiologically or pharmacologically active substances intended for use in the treatment, prevention, diagnosis, cure or mitigation of disease or illness, or that provide some degree of nutritional, physiological or therapeutic benefit to an animal when consumed. The term refers more particularly to a substance that affects beneficially one or more target functions in the body, in a way that is either an improved state of health or well-being and/or reduction of risk of disease. Non-limiting examples include drugs, botanical extracts, enzymes, hormones, proteins, polypeptides, antigens, nutritional supplements such as fatty acids, antioxidants, vitamins, minerals, as well as other pharmaceutically or therapeutically useful compounds. A functional ingredient in the context of the present invention refers to an ingredient included in the delivery system of the invention in addition to those ingredients that constitute the gel matrix itself. In the context of the present invention, antacids are a functional ingredient.

The term "antacid" as used herein, refers to a compound capable of increasing gastric pH and includes, but is not limited to, a variety of inorganic salts as well as naturally

occurring substances such as glycine. In one embodiment of the present invention, an antacid refers to a compound that is capable of increasing the pH of 10 mL of 0.5 N HCl (5 mEq) to at least pH 3.5 after 10 minutes of stirring.

The term "nutritional supplement," as used herein, refers to a substance that exerts a physiological effect on an animal. Typically, nutritional supplements fulfil a specific physiological function or promote the health or well-being of the consumer.

The terms "botanical extract" and "botanical," as used interchangeably herein, refer to a substance derived from a plant source. Non-limiting examples include echinacea, Siberian ginseng, ginko biloba, kola nut, goldenseal, golo kola, schizandra, elderberry, St. Johns Wort, valerian, ephedra and the like.

The term "drug," as used herein, refers to a pharmacologically active substance that exerts a localised or systemic effect or effects on an animal.

The term "pro-drug," as used herein, refers to an inactive precursor of a drug that has to be metabolised or otherwise processed *in vivo* following administration in order to exhibit pharmacologic activity.

The terms "subject" and "patient" as used herein refer to an animal in need of treatment.

The term "animal," as used herein, includes, but is not limited to, mammals (including humans), birds and reptiles.

The term "treatment," as used herein, refers to an intervention performed with the intention of improving a patient's status. The improvement can be subjective or objective and is related to the alleviation of the symptoms associated with a condition being treated.

As used herein, the term "about" refers to a +/-10% variation from the nominal value. It is to be understood that such a variation is always included in any given value provided herein, whether or not it is specifically referred to.

ANTACID DELIVERY SYSTEMS

The antacid delivery systems according to the present invention are gel delivery systems that comprise one or more antacids dispersed in an ingestible matrix. The delivery system may further comprise one or more other functional ingredients. The matrix of the delivery system provides for substantially uniform and complete dispersion of the antacid(s) (and other functional ingredients) and helps to minimise degradation of heat labile functional ingredients during manufacturing. The matrix of the delivery system further provides for minimised degradation of the functional ingredients during subsequent storage of the final delivery system. The antacid delivery systems are useful, for example, to relieve symptoms of acid indigestion, heartburn, gastroesophageal reflux, and the like.

While the primary functional ingredient in the delivery system is one or more antacids, the delivery system can be formulated to accommodate specific combinations of other functional ingredients that are selected as nutritional supplements and/or to provide a specific physiological effect, for example, weight loss, sexual health, cardiovascular health, joint health, bone health, anti-oxidant effects, appetite suppression, thermogenesis, memory enhancement, performance enhancement, digestive health, or to help prevent colds or fight infection. In one embodiment, the delivery system comprises one or more other functional ingredients that complement or enhance the function of antacids within the body.

The delivery system of the present invention comprises one or more antacids (and optionally other functional ingredients) substantially uniformly dispersed within a gel matrix which comprises 1) one or more hydrocolloids; 2) a sugar component and 3) a solvent component. The selection of appropriate hydrocolloid(s) as described herein in amounts within the ranges indicated results in a matrix that readily retains the solvent component and thereby helps to prevent separation of the solvent from other components of the matrix. Additives, such as natural or artificial flavourings, colourings, pH modifying agents, buffers and sweeteners can be included in conventional amounts in the matrix. The matrix may also include one or more sources of monovalent cations or divalent cations, if required, to allow for proper set-up of the

matrix. If insufficient water is provided by the various components selected to formulate the matrix, additional water may be added to the matrix as necessary to provide the desired final moisture content within the range indicated below.

The delivery system may further comprise one or more compounds that act to enhance the bioavailability of the antacid(s) and other functional ingredients (*i.e.* "bioavailability enhancers"), as discussed in more detail below.

Due to the substantially uniform and complete dispersion of the antacid(s) within the matrix, the delivery systems of the invention are suitable for division into sub-units. For example, if a single unit of a delivery system is divided into three subunits, each subunit will contain a third of the dose of the original unit. Such division would not be possible with other delivery systems in which the functional ingredients are not evenly dispersed.

As indicated above, the matrix of the delivery systems provides for minimised degradation of functional ingredients during the preparation of the matrix and the storage of the final delivery systems. The use of relatively low temperatures in the preparation of the matrix, when compared to typical manufacturing procedures for confectioneries, ensures that the functional ingredients are not degraded by excessive heat. In accordance with the present invention, the functional ingredients are added to the other components of the matrix to prepare the delivery system at a temperature of 100°C or less. In one embodiment of the present invention, the entire preparation process takes place at or below 100°C. In another embodiment, the delivery systems are prepared at or below a temperature of 75°C. In another embodiment, the delivery systems are prepared at or below a temperature of 70°C. In a further embodiment, the delivery systems are prepared at or below a temperature of 65°C. Low temperatures can be employed in the preparation of the delivery system because the matrix is formulated to be flowable at low temperatures by selection of appropriate ingredients as described herein. In one embodiment of the invention, the matrix is flowable at or above 45°C. In another embodiment, the matrix is flowable at or above 35°C.

The delivery systems of the present invention are intermediate moisture products and maintain a low interaction with water during and after preparation of the matrix,

which can also contribute to the stability of some of the functional ingredients dispersed therein. Although the actual amount of moisture and final water activity (a_w) of an intermediate moisture food has not been defined precisely, general opinion is that an intermediate moisture product should have a moisture content between about 10% and about 40% by weight and an a_w below about 0.9 (see, S. Hegenbart, "Exploring Dimensions in Intermediate Moisture Foods," (1993) *Food Product Design,* Weeks Publishing Company, Northbrook, IL). In accordance with the present invention, therefore, the final moisture content of the delivery systems is between about 10% and about 40%. In one embodiment, the final moisture content of the delivery systems is between about 10% and about 30%. In another embodiment, the final moisture content of the delivery systems is between about 11% and about 25%. In other embodiments, the moisture content is between about 13% and about 20%, and between about 14% and about 18%.

In addition, the delivery systems of the present invention have an a_w below about 0.9. In one embodiment of the invention, the water activity of the final delivery systems is below about 0.85. In another embodiment, the water activity of the final delivery systems is below about 0.8. In a further embodiment, the water activity is below about 0.7. In another embodiment, the water activity is below about 0.6. Alternatively, the water activity of the final delivery systems may be described as being between about 0.45 and about 0.7. In another embodiment, the water activity is between about 0.5 and about 0.65.

For those functional ingredients that are susceptible to degradation, for example, due to heat lability, degradation during the process of preparing the matrix of the delivery systems is minimised. In one embodiment, degradation of the functional ingredients during preparation of the matrix is less than about 20%. In another embodiment, degradation of the functional ingredients during preparation of the matrix is less than about 15%. In other embodiments, degradation of the functional ingredients during preparation is less than about 10%, less than about 5%, less than about 3% and less than about 2%.

Degradation of the functional ingredients during storage of the final delivery systems under normal storage conditions (*i.e.* at temperatures of 30°C or below) is also minimised. In accordance with the present invention, therefore, degradation of the functional ingredients during storage of the delivery systems under normal conditions is less than about 20%. In one embodiment, degradation of the functional ingredients during storage is less than about 15%. In other embodiments, degradation of the functional ingredients during storage is less than about 10%, less than about 5%, less than about 3% and less than about 2%.

The matrix to be used in the delivery systems of the invention can be formulated to have a final pH in the range of about 2.5 to about 9.0. As will be appreciated by one skilled in the art, however, selection of the final pH for the matrix will be influenced by the properties of the functional ingredients to be included in the final delivery system. Thus, for the antacid delivery systems of the invention, the matrix is formulated such that the delivery systems have a final pH in the range of about 5.0 to about 9.0. In one embodiment, the matrix is formulated such that the delivery systems have a final pH in the range of about 5.5 to about 9.0. In another embodiment, the matrix is formulated such that the delivery systems have a final pH in the range of about 6.0 to about 9.0. In further embodiments, the matrix is formulated such that the delivery systems have a final pH in the range of about 6.5 to about 9.0 and about 7.0 to about 9.0.

In their final form, the delivery systems of the present invention are semi-solid, intermediate moisture systems, having some properties clearly identified with those of jellies and some properties that are similar to the jujube variety of confectioneries. In the context of the present invention, the term "semi-solid" indicates that the delivery system has properties that, depending on the measurement, are a mixture of solid and liquid behaviours. The matrix of the delivery systems, therefore, is formulated to be semi-solid at normal room temperature. In the event, however, that the matrix liquefies due to exposure to elevated temperatures, the formulation of the matrix is such that no phase separation of the components occurs and the matrix can be readily re-solidified by cooling (for example, by cooling to temperatures of around 4°C). The reformed product maintains the substantially uniform dispersion of the antacids (and

other optional functional ingredients) contained therein. In one embodiment of the present invention, the delivery systems are formulated such that the matrix is a semi-solid at temperatures at or below about 40°C. In another embodiment, the delivery systems are semi-solid at or below about 35°C. In other embodiments, the delivery systems are semi-solid at or below about 30°C and at or below about 25°C.

The gel delivery systems according to the present invention are suitable for administration to both human and non-human animals. One skilled in the art will appreciate that each delivery system can be formulated differently according to the type of animal to which it is to be administered. For example, for administration to an animal such as a cat or a dog, meat or fish-based flavours may be added. For administration to a human, the delivery system may be formulated, for example, as a confectionery using fruit-based or other confectionery flavours. The delivery systems are especially suited for oral administration due to their palatability. Additionally, due to the highly portable format, the delivery systems are simple and convenient to administer and to consume for both humans and other animals.

The texture, physical attributes, form and shape of the matrix as described below, can be varied by altering the ratio of ingredients within the given ranges using the methods described herein or by methods familiar to a worker skilled in the art.

1. The Matrix

As indicated above, the delivery systems of the invention comprise one or more antacids dispersed in a matrix that comprises 1) one or more hydrocolloids; 2) a sugar component and 3) a solvent component. For the purposes of the present invention, "hydrocolloids" can be divided into carbohydrate-based hydrocolloids and non-carbohydrate based hydrocolloids. The delivery system of the present invention can comprise one or more carbohydrate-based hydrocolloids, one or more non-carbohydrate based hydrocolloids, or a combination of one or more carbohydrate-based hydrocolloids with one or more non-carbohydrate based hydrocolloids.

1.1 Hydrocolloid

The matrix according to the present invention comprises one or more hydrocolloids that perform the functions of water binding and gelation and contribute to the overall texture and body of the gel matrix. Hydrocolloids can also be used to improve and/or stabilise the texture of a food product while inhibiting crystallisation.

Hydrocolloids are hydrophilic polymers of vegetable, animal, microbial or synthetic origin. Non-carbohydrate based hydrocolloids are typically animal-derived, a representative example being gelatine (hydrolysed collagen). Carbohydrate-based hydrocolloids are typically plant derived and include starches (and other amylaceous ingredients) and polysaccharide-based gums. An "amylaceous ingredient" as used herein refers to a food-stuff that contains a preponderance of starch and/or starch-like material. Examples of amylaceous ingredients include cereal grains and meals or flours obtained upon grinding cereal grains such as corn, oats, wheat, milo, barley, rice, as well as the various milling by-products of these cereal grains such as wheat feed flour, wheat middlings, mixed feed, wheat shorts, wheat red dog, oat groats, hominy feed, and other such material. Other sources of amylaceous ingredients include tuberous foodstuffs, such as potatoes, tapioca, and the like.

Suitable starches for use in the delivery systems are typically modified starches derived from a variety of plant sources such as, for example, corn, waxy corn, wheat, rice, tapioca, potato, pea and other sources known in the art. Modified starches are known in the art refer to starches that have been physically or chemically altered to improve their bioactive characteristics. Suitable modified starches include, but are not limited to, pre-gelatinised starches, low viscosity starches (such as dextrins, acid-modified starches, oxidized starches and enzyme modified starches), derivatised starches, stabilised starches (such as starch esters and starch ethers), cross-linked starches, starch sugars (such as glucose syrup, dextrose and isoglucose) and starches that have been submitted to a combination of treatments (such as cross-linking and gelatinisation) and mixtures thereof.

Examples of suitable polysaccharide-based gums that can be used in the delivery systems include, but are not limited to, Konjac, tragacanth gum, guar gum, acacia

gum, karaya gum, locust bean gum, xanthan gum, agar, pectin, carageenan, gellan, alginate, and various cellulose gums. Suitable cellulose gums for use in the preparation of the matrix are typically modified cellulose gums including, for example, methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methylcellulose acetate, hydroxyethyl methylcellulose, hydroxyethylcellulose acetate, hydroxyethyl ethylcellulose and combinations thereof.

The use of hydrocolloids is well-known in the art and many hydrocolloids for use in products for human or animal consumption are available commercially, for example, gelatines from Leiner Davis, various polysaccharide gums and blends manufactured by CP Kelco, the Ticagel® range of hydrocolloids from TIC Gums, modified starches from A.E. Staley and a range of modified celluloses known as Methocel Food Gums manufactured by Dow Chemical Company.

In one embodiment of the present invention, the gel matrix comprises gelatine. Gelatine is defined generally using a "Bloom value" which indicates the strength of the gel formed under certain circumstances using the gelatine. In the preparation of confectionery, when a harder gel is desired, gelatine having a higher Bloom value is used. Conversely, when the final product is required to be more flowing, gelatine having a lower Bloom value is used. One skilled in the art will appreciate that the water holding capacity of gelatine alone is lower than that of a combination of gelatine with another hydrocolloid, such as gellan or pectin. Thus, the use of gelatine alone as the hydrocolloid in the delivery system may necessitate the use of a higher amount of gelatine to achieve the desired gelation/texture of the matrix, than when gelatine is used in combination with one or more other hydrocolloids. When the hydrocolloid in the matrix of the present invention comprises gelatine, the Bloom value (BL) is generally about 100 to 260 BL. Combinations of gelatines with different Bloom values also can be used. The gelatine can be derived from a variety of sources, for example, beef, pork, chicken or fish gelatine (or a combination thereof) may be used.

When the gel matrix comprises gelatine, the gelatine can be combined with one or more other hydrocolloids to impart different characteristics to the matrix. For example, combinations of gelatine with gellan or gelatine with pectin provide a good texture to the matrix. Addition of a modified starch to one of these combinations also provides textural improvements.

When combinations of gelatine and gellan or pectin are used in the preparation of the matrix, the ratio of gelatine:gellan or gelatine:pectin is typically in the range between about 15:1 to about 40:1. These relative amounts provide a cohesive structure to the delivery system.

Similarly, a combination of a modified starch with one or more other hydrocolloids can impart certain desirable features to the matrix, for example, modified starch can contribute to the structural integrity of the matrix and its low set temperature. It can also provide heat stability to the finished product as well as the ability to bind a limited quantity of fats/oils if required.

The use of combinations of modified starches and modified celluloses as the hydrocolloid component of the matrix is also contemplated by the present invention as discussed below in Section 1.5.

An example of a suitable type of modified starch for inclusion in the matrix is one that is able to fully hydrate and develop its viscosity in the presence of the other matrix-forming components at a temperature below 100°C, for example at a temperature of, or below, 70°C. Such starches are often referred to as "low set temperature" starches. While the majority of carbohydrates hydrate upon heating, certain starches, which are commercially available and are known in the art as "cold set" or "pre-gelatinised" starches are capable of hydrating at room temperature and are also suitable for use in the gel matrix.

One skilled in the art will appreciate that the viscosity development of the selected hydrocolloid or hydrocolloid mixture should allow for sufficient ease of mechanical handling and pumping during production as well as allowing sufficient time to incorporate all the ingredients and to mould the final product before it sets.

In addition, it will be understood that the hydrocolloid(s) to be used in the gel matrix will depend on the desired final pH of the matrix, the particular texture and consistency required for the final product and, if more than one hydrocolloid is used, the interaction of the hydrocolloids. Certain combinations of hydrocolloids are known in the art to provide synergistic effects, for example, the combination of xanthan (which does not gel well alone) with Konjac, or carageenan and Konjac.

The type of hydrocolloid, or mixture of hydrocolloids, used can also affect the set temperature of the matrix. For example, the use of a gelatine/gellan mixture or a gelatine/pectin mixture provides a set temperature around 35°C, whereas the use of carageenan or locust bean gum will result in a set temperature closer to 60°C. Thus, the choice of hydrocolloid(s) for use in the matrix is also dependent upon the properties of the functional ingredient(s) to be incorporated into the delivery system. Functional ingredients that are unstable at higher temperatures will require the selection of a hydrocolloid or mixture of hydrocolloids that have a low set temperature, whereas functional ingredients that are more stable can be used with hydrocolloid(s) having a higher set temperature.

The use of hydrocolloids in intermediate moisture products is well known in the art and a skilled technician would readily be able to select an appropriate hydrocolloid or mixture of hydrocolloids for use in the delivery systems of the invention. In one embodiment of the present invention, the delivery system comprises one or more modified starch, alone or in combination with one or more other hydrocolloid. Non-limiting examples of hydrocolloids suitable for use with modified starch include gelatine; gellan and gelatine; pectin and gelatine; gellan, gelatine and one or more cellulose or modified cellulose; and pectin, gelatine and one or more cellulose or modified cellulose. In another embodiment of the present invention, the delivery system comprises gelatine, alone or in combination with one or more other hydrocolloid. Non-limiting examples of hydrocolloids suitable for use with gelatine include one or more modified starch; gellan; pectin; cellulose or modified cellulose; gellan and one or more modified starch; pectin and one or more modified starch; gellan and one or more cellulose or modified cellulose; pectin and one or more cellulose or modified cellulose; gellan, one or more modified starch and one or more

cellulose or modified cellulose; and pectin, one or more modified starch and one or more cellulose or modified cellulose. In a further embodiment of the present invention, the delivery system comprises pectin in combination with one or more other hydrocolloid. Non-limiting examples of hydrocolloids suitable for use with pectin include gelatine; gelatine and one or more modified starch; gelatine and one or more cellulose or modified cellulose; and gelatine, one or more modified starch and one or more cellulose or modified cellulose.

The total amount of hydrocolloid(s) incorporated into the matrix is generally between about 0.1% and about 17% by weight. In one embodiment, the total amount of hydrocolloid(s) in the matrix is between about 0.6% to about 17% by weight. In a further embodiment, the total amount is between about 0.6% and about 15% by weight. In another embodiment, the total amount is between about 0.5% and about 10% by weight.

The selection of the actual amount of hydrocolloid(s) from within the ranges provided above to be included in the matrix will be dependent upon the type of hydrocolloid(s) being used and on the desired texture of the final product. Determination of this amount is considered to be within the ordinary skills of a worker in the art.

In one embodiment of the invention, the matrix comprises one or more modified starch in an amount between about 0.5% and about 10.0% by weight, for example, between about 1.7% and about 8.0%. In another embodiment, the matrix comprises gelatine in an amount between about 0.1% and about 10% by weight, for example between about 1.0% and 9.0%. In a further embodiment, the matrix comprises a polysaccharide-based gum in an amount between about 0.1% and about 5.0% by weight, for example, between about 0.2% and about 2.0%. In still another embodiment, the matrix comprises one or more modified cellulose in an amount between about 0.1% and about 3% by weight, for example, between about 0.6% and 1.5%.

In a specific embodiment of the invention, the matrix comprises a combination of one or more modified starch in an amount between about 0.5% and about 10.0% by weight, gelatine in an amount between about 0.1% and about 10.0% by weight, and a

polysaccharide-based gum in an amount between about 0.1% and about 2.0% by weight.

1.2 Sugar Component

Sugar is generally used in a confection primarily for sweetness; however, it is known in the art that sugar can also play an important role in the physical properties of a matrix, such as crystallinity, gel strength, bodying/texture, humectancy, and water activity.

The sugar component of the matrix comprises one or more sugars, sugar syrups, sugar alcohols and/or sugar alcohol solids. Examples include, but are not limited to, sugars such as sucrose, glucose, xylose, ribose, maltose, galactose, dextrose, and fructose; syrups such as corn syrups, hydrogenated glucose syrups, high fructose corn syrups; polydextrose; and sugar alcohols such as isomalt, maltitol, sorbitol, lactitol, and mannitol. The latter are also often in the form of syrups. One skilled in the art will appreciate that if a sugar or sugar alcohol solid is used in the matrix, it should be first dissolved, for example, by heating in water or in another syrup, prior to being added to the mixture.

When the sugar component comprises dextrose, it is generally provided in the form of a corn syrup. Corn syrups are prepared by hydrolysis of starch and are characterised by dextrose equivalent (D.E.) values such that they are classified as low, medium or high D.E. syrups, with high D.E. syrups having a high concentration of dextrose and low D.E. syrups having a low concentration of dextrose. In one embodiment of the present invention, the sugar component used in the preparation of the matrix comprises a corn syrup and/or a high fructose corn syrup. Suitable corn syrups are typically those with a D.E. between 20 D.E. and 99 D.E., for example, between about 40 D.E. and 70 D.E.

Various corn syrups are commercially available. For example, 62 D.E. 1600 Corn Syrup (Casco Inc./ Canada Starch Operating Co. Inc.), SWEETOSE 4300 corn syrup (a 63 D. E. corn syrup; A. E. Staley Manufacturing Company; Decatur, IL) and

Clearsweet® 63/43 IX corn syrup (a 63 D. E. corn syrup; Cargill / North America Sweeteners).

Combinations of sugars or sugar syrups are also suitable for use in the preparation of the matrix. Examples of suitable combinations of syrups include, but are not limited to, isomalt syrup and high fructose corn syrup, a high D.E. corn syrup and high fructose corn syrup and maltitol syrup and high fructose corn syrup.

One skilled in the art will appreciate that the total amount of the sugar component in the matrix will vary depending upon the type(s) of sugar used. For example, when sugar syrups are used, lower viscosity sugar syrups will produce a matrix with less body and lower rigidity. The total amount of the sugar component present in the matrix is about 10% to about 60% by weight.

In one embodiment of the present invention, the sugar component comprises a mixture of sugar syrups. In another embodiment, the sugar component comprises a mixture of sugar syrups in a total amount of between about 15% and about 55% by weight of the delivery system. In a further embodiment, the sugar component comprises a mixture of sugar syrups in a total amount between about 25% and about 55% by weight of the delivery system.

1.3 Solvent Component

The primary role of the solvent component of the matrix is to dissolve or disperse the functional ingredients to allow for substantially uniform and complete incorporation of these ingredients into the matrix. The solvent also provides for improved flow characteristics of the mixture and functions somewhat as a humectant. In accordance with one embodiment of the present invention, the antacid(s) and/or other functional ingredients are added to the solvent component prior to combining with the remaining components of the matrix.

The solvent used in the preparation of the matrix is typically colourless and non-volatile with no strong odour or flavour and is substantially miscible with water and/or alcohols. In accordance with the present invention, the solvent component

comprises one or more polyhydric alcohol. The term "polyhydric" as used herein means that the compound contains two or more hydroxyl groups. Examples of suitable polyhydric alcohols include, but are not limited to, glycerol and/or its lower alkyl ester derivatives, propylene glycol, and short chain polyalkylene glycols, such as polyethylene glycol, and mixtures thereof. As will be apparent to one skilled in the art, certain polyhydric alcohols may also function somewhat as sweeteners.

In one embodiment of the present invention, the solvent component comprises glycerol. In another embodiment, the solvent component comprises a mixture of glycerol and a short chain polyalkylene glycol. In a further embodiment, the solvent component comprises a mixture of glycerol and propylene glycol.

Typically, the delivery system according to the present invention contains about 5% to about 50% by weight of the solvent component. In one embodiment, the delivery system contains about 5% to about 38% by weight of the solvent component. In an alternate embodiment, the delivery system contains about 10% to about 50% by weight of the solvent component. In a further embodiment, the delivery system contains about 20% to about 48% by weight of the solvent component. In other embodiments, the delivery system contains between about 15% and about 50%, between about 15% and about 40% and between about 15% and 35% by weight of the solvent component.

1.4 Water

As indicated above, the delivery system according to the present invention has a final moisture content between about 10% and about 40% and a water activity below about 0.9. In one embodiment, the final moisture content of the delivery system is between about 10% and about 30% and the water activity is below about 0.7. It will be readily apparent to one skilled in the art that the appropriate amount of water may be provided by one or more of the various components of the system, for example, a sugar syrup, a hydrated starch or a hydrated hydrocolloid, or additional water may need to be added separately. Additional water can be provided alone or as a solution containing other additives, for example, as a buffer solution or as a solution containing a sweetener, flavouring or colouring. The total amount of water from the

one or more sources will be sufficient to provide the final delivery system with a moisture content and water activity within the ranges indicated above.

1.5 Other Additives

The gel matrix can optionally contain other additives such as flavourings, colourings, additional sweeteners, modified vegetable gums or celluloses, mono- or divalent cations, or a combination thereof. It will be readily apparent that additives for inclusion in the matrix should be selected such that they do not affect the properties of the matrix, do not exhibit substantial reactivity with the functional ingredients in the matrix, and are stable during preparation of the matrix.

The sweetener can be selected from a wide variety of suitable materials known in the art. Representative, but non-limiting, examples of sweeteners include xylose, ribose, sucrose, mannose, galactose, fructose, dextrose, maltose, partially hydrolysed starch, lactose, maltodextrins, hydrogenated starch hydrolysate and mixtures thereof. In addition to these sweeteners, polyhydric alcohols such as sorbitol, mannitol, xylitol, and the like may also be incorporated. Alternatively, an artificial sweetener or a blend of artificial sweeteners can be used. Examples of suitable artificial sweeteners include, for example, sucrose derivatives (such as Sucralose), amino acid based sweeteners, dipeptide sweeteners, saccharin and salts thereof, acesulfame salts (such as acesulfame potassium), cyclamates, steviosides, dihydrochalcone compounds, thaumatin (talin), glycyrrhizin, aspartame, neotame, alitame, and mixtures thereof.

When an additional sweetener is used, it can be used in amounts as low as 0.01% by weight. The actual amount of sweetener required will be dependent on the type of sweetener selected and on the desired sweetness of the final product. Amounts of various sweeteners to be added to food products are well known in the art. When a natural sweetener is used, the total amount of the sugar component, which forms a structural part of the matrix, and additional sweetener(s) in the matrix, however, remains less than 60% by weight. In one embodiment of the invention, the matrix comprises one or more additional sweeteners. In another embodiment, the matrix comprises one or more artificial sweeteners.

Suitable flavourings that can be added to the delivery system are known in the art and include, both synthetic flavour oils and oils derived from various sources, such as plants, leaves, flowers, fruits, nuts, and the like. Representative flavour oils include spearmint oil, peppermint oil, cinnamon oil, and oil of wintergreen (methylsalicylate). Other useful oils include, for example, artificial, natural or synthetic fruit flavours such as citrus oils including lemon, orange, grape, lime and grapefruit, and fruit essences including apple, strawberry, cherry, pineapple, banana, raspberry and others that are familiar to a worker skilled in the art. A wide variety of synthetic flavourings suitable for inclusion in the matrix are known in the art and are commercially available. The amount of flavouring agent employed is normally a matter of preference subject to such factors as concentration/dilution of the flavour stock, flavour type, base type and strength desired. In general, amounts of about 0.01% to about 5.0% by weight of a final product are useful.

Colourings suitable for use in foodstuffs are well known in the art and can be optionally included in the matrix to add aesthetic appeal. A wide variety of suitable food colourings are available commercially, for example, from Warner Jenkins, St. Louis, MO. Where a synthetic colouring agent is used in the matrix, the amount ranges from about 0.01% to about 2% by weight. A worker skilled in the art will appreciate that when a colouring agent derived from a natural source is used in the matrix, an increased amount of the colouring agent is generally required to achieve the same effect as a synthetic colouring agent.

The present invention also contemplates that modified vegetable gums or modified or unmodified celluloses may be included in the matrix in order to improve the texture, body, lubricity and/or elasticity of the matrix. These compounds can be used, for example, to increase the viscosity of the delivery system if it is warmed, thus reducing potential melting and lessening water activity which will help to improve the stability of the system in the event it is left in an excessively hot environment. Examples of modified vegetable gums or modified celluloses are provided above. Unmodified celluloses are also contemplated and are known in the art. Examples of cellulose include Solka-Flo® from International Fibre Corporation, North Tonawanda, New York, and powdered Avicel® microcrystalline cellulose from FMC Biopolymers,

Philadelphia, PA. Modified vegetable gums can be included in the matrix in amounts between about 0.01% and 2.0% by weight, for example between about 0.1% and about 1.5%. Modified or unmodified celluloses, or mixtures thereof, can be included in the matrix in amounts between about 0.1% and about 10.0% by weight, for example, between about 0.6% and about 5.0%.

If necessary; the matrix can also comprise one or more sources of monovalent cations and/or divalent cations (in addition to the antacids) to help facilitate gelation of the matrix. Suitable sources of mono- and divalent cations for incorporation into food products are known in the art and are commercially available. Non-limiting examples include mono- or divalent salts, such as sodium or potassium chloride and potassium citrate. Mono- or divalent salts can be added to the matrix, if required, in an amount between, for example, about 1% and about 5% by weight.

2. Antacids

A number of antacids can be included in the delivery systems of the invention. Examples of acceptable antacids include, but are not limited to, the following: aluminium salts (such as alumina, aluminium carbonate, aluminium hydroxide and aluminium phosphate); bentonite; bismuth salts (such as bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate and bismuth subsalicylate); calcium carbonate; calcium phosphate; citric acid and salts thereof (such as potassium citrate and sodium citrate); dihydroxyaluminium aminoacetate (also known as aluminium glycinate); dihydroxyaluminium sodium carbonate; glycine; hydrotalcite; magnesium salts (such as magnesia, magnesium alginate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium phosphate, magnesium aluminium silicate and magnesium trisilicate); magaldrate; milk solids; potassium salts (such as potassium bicarbonate and potassium phosphate); sodium bicarbonate; sodium polyhydroxy aluminium monocarbonate hexitol complex; sucralfate (a basic aluminium salt of sucrose octasulphate); tartaric acid and salts thereof (such as sodium tartrate and sodium potassium tartrate); tricalcium phosphate and zeolite, or combinations thereof.

Many of the above compounds are commercially available in dried gel and powder formats, which are suitable for use in the preparation of the delivery systems. Aluminium hydroxide is also available as an aluminium hydroxide-hexitol stabilised polymer and as aluminium hydroxide-sucrose powder.

Pre-processing of the antacids by micronisation or pre-coating is not required for the delivery systems of the present invention, however, if desired, micronised or pre-coated antacids can be employed. Various coatings are known in the art that would be suitable for the purposes of the present invention (see, for example, U.S. Patent No. 4,882,154). Micronisation of minerals is also standard in the art.

Up to 40% by weight of the selected antacid(s) can be included in the delivery system of the invention. In one embodiment, up to about 35% by weight of the selected antacid(s) is included in the delivery system. In another embodiment, up to about 30% by weight of the selected antacid(s) is included. In an alternate embodiment, the delivery systems comprise between about 10% and about 30% by weight of the antacid(s). In a further embodiment, the delivery systems comprise between about 15% and about 30% by weight of the antacid(s).

3. *Other Functional Ingredients*

The present invention contemplates that one or more additional functional ingredients may be added to the antacid delivery system. A wide variety of functional ingredients are suitable for inclusion in the delivery system, including, but not limited to, therapeutic compounds, nutritional supplements that fulfil a specific physiologic function or promote the health and/or well-being of the consumer, botanicals, herbal extracts, and the like. For example, the one or more functional ingredients included in the delivery system can be a nutritional supplement. Illustrative, but non-limiting, examples of suitable nutritional supplements include, probiotic bacteria, prebiotics, vitamins, enzymes, co-enzymes, cofactors, antioxidants, minerals and mineral salts, amino-acids and amino acid derivatives (for example, dimethylglycine), peptides, proteins, gums, carbohydrates, phytochemicals, dextroses, phospholipids, other trace nutrients, oxygenators, brain-stimulating substances, energy providers, metabolic intermediates, hormones, botanical extracts, fatty acids (for example, linoleic acid or

conjugated linoleic acid), oat beta-glucan and other functional fibres, carnitine, bicarbonate and citrate.

The selection of appropriate and compatible combinations of functional ingredients can be made readily by the skilled technician. As is known in the art, certain combinations of functional ingredients are incompatible due to undesirable interactions between the ingredients, for example, interactions that alter absorption, renal elimination, or hepatic metabolism of one or more of the functional ingredients, or that result in additive effects or toxicities. Accordingly, selection of appropriate combinations of functional ingredients can be made by the skilled worker based on knowledge in the art and publicly available information regarding contraindications of certain combinations (see, for example, *The A-Z Guide to Drug-Herb and Vitamin Interactions,* Schuyler W. Lininger (ed.) (1999) Three Rivers Press (CA); *Mosby's Handbook of Drug-Herb & Drug-Supplement Interactions,* R. Harkness & S. Bratman (2002), Mosby; and the Mayo Clinic website).

Combinations of functional ingredients that are designed to achieve a specific physiological purpose are also contemplated for inclusion in the delivery system. A wide variety of such combinations of functional ingredients are known in the art for providing specific physiological benefits and are suitable for inclusion in an antacid delivery system of the invention. Non-limiting examples are provided in Table 1.

Table 1: Exemplary Functional Ingredients and Combinations Thereof

Physiological Effect	*Suggested Functional Ingredients*
Energy enhancement	Ginseng, chromium picolinate, chromium chelate, Rhodiola crenulata
Weight loss	Caffeine, ephedra, conjugated linoleic acids (CLA), amino acids
Thermogenesis	Caffeine, tocopherols, Citrus aurantium, ephedra alkaloids,
Memory enhancement	Ginkgo biloba, goto kola

Physiological Effect	*Suggested Functional Ingredients*[1]
Sexual health	Yohimbe, Kubu pepper
Antioxidant	Vitamin E, Vitamin C, Alpha Lipoic Acid (ALA)
Bone health	Inulin, fructooligosaccharides, Vitamin D, Vitamin K, Vitamin C, magnesium, phosphorus, zinc, copper, boron, manganese, selenium, fluoride, isoflavones
Joint health	Methylsulphonylmethane (MSM), glucosamine, chondroitin
Cold prevention	Echinacea, zinc, vitamin C
Vitamin and/or mineral supplementation	B-Vitamin complex, D vitamins, Vitamin C, Vitamin co-factors
Dietary supplements	Essential fatty acids, amino acids
Muscle enhancement	Creatine, dimethylglycine, pregnenolone, amino acids
Probiotics	Acidiphilus, Bifidus, prebiotics,
Digestive aids	Bromelain, papain, lipases, probiotics,
Anti-aging	Omega-3 fatty acids, lignan, S-adenosyl methionine(SAMe), melatonin
Seniors health	Omega-3 fatty acids, SAMe
Women's health	Soy isoflavanones
Cardiovascular health	Arginine, Siberian Ginseng, Vitamin B6, CoQ10, Rhodiola crenulata

[1]Delivery systems may contain one, or a combination, of the listed functional ingredients

In one embodiment of the present invention, the delivery system comprises one or more additional functional ingredients that complement or enhance the function of antacids within the body. Such functional ingredients include, for example, drugs, therapeutic compounds, nutritional supplements, botanicals or herbal extracts, and the like.

Examples of suitable classes of drugs and therapeutic compounds for incorporation into the delivery systems include, but are not limited to, antiflatulent/ antifoaming agents, H_2 receptor antagonists (also known as H_2 blockers or histamine blockers), proton pump inhibitors, antispasmodic agents, local anaesthetics, analgesics and anti-inflammatories (including non-steroidal anti-inflammatories or NSAIDs), and combinations thereof. Drugs can be included in their active form, or where appropriate, as pro-drugs.

Exemplary drugs include the antiflatulent, dimethicone (also known as simethicone or polydimethylsiloxane); the antidiarrhoeal, glycopyrrolate; the H_2 receptor antagonists, cimetidine, famotidine, nizatidine and ranitidine; the proton pump inhibitors, omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole; the antispasmodic agents dicyclomine and scopolamine; the local anaesthetics, lidocaine, benzocaine and oxethazaine, and the NSAIDs, salicylic acid and its derivatives (such as aspirin (acetyl salicylic acid)), acetominophen, and ibuprofen.

The drug metaclopramide, which increases gastric emptying, is also useful in combination with antacids and can be included in the delivery systems with an antacid, alone or in combination with other functional ingredients.

Sucralfate, when not used as an antacid itself, can also be included in the delivery systems in combination with an antacid, and optionally one or more other functional ingredients. Sucralfate is widely used to treat peptic and duodenal ulcers, gastritis and the like.

The present invention also contemplates the inclusion in the delivery systems of one or more so-called "rafting agents." Rafting agents are typically alginate-based compounds, such as alginic acid and sodium alginate, which precipitate in the presence of gastric acid to form a neutral gel. Magnesium and potassium salts of alginic acid are also useful. Pectin can also be used as a rafting agent. Thus, the delivery systems of the invention can comprise pectin either as a structural component of the matrix, as indicated above, or as a functional ingredient.

Chelating agents, such as EDTA, can also be included in the delivery system. For example, inclusion of EDTA in delivery systems comprising antacid(s) in combination with cimetidine and an alginate-based rafting agent can help to minimise oxidation of the cimetidine. EDTA is generally included as a salt, for example, as disodium EDTA, although the free acid may also be used.

Other functional ingredients suitable for incorporation into the delivery systems include prebiotics, vitamins, antioxidants, minerals and mineral salts, amino-acids and amino acid derivatives, phytochemicals, hormones, botanical extracts, oat beta-glucan or other functional fibres, and combinations thereof.

For example, deglycyrrhizinated liquorice (DGL) is known to help stimulate the stomach's protective abilities and can be included in the delivery systems. Activated charcoal acts as an antiflatulant and can also be included in the delivery systems. Carboxymethylcellulose, for example as sodium carboxymethylcellulose, is also often used in combination with antacids. Thus, the delivery systems of the invention can include carboxymethylcellulose as a structural component of the matrix, as indicated above, or as a functional ingredient.

When the antacid is a calcium salt, vitamins may be added to the delivery system. For example, Vitamin D (including vitamin D, cholecalciferol (vitamin D_3), ergocalciferol (vitamin D_2) and its biologically active metabolites and precursors such as, 1α,25-dihydroxyvitamin D; 25-OH vitamin D, its biological precursor; and 1α-hydroxyvitamin D), Vitamin C and Vitamin K, or combinations thereof.

If desired, micronised or pre-coated forms of the above-described functional ingredients may be used.

Typically, the total amount of antacid(s) and other functional ingredients constitute up to about 40% by weight of a delivery system. Thus, the amount of other functional ingredient(s) included in the delivery system will be dependent on the amount of antacid(s) that is to be incorporated. In all cases, however, the amount of the one or more antacids included in the delivery system is greater on a weight % basis than the amount of any other single functional ingredient. In one embodiment of the present

invention, the delivery systems incorporate between about 0.01% and about 20% by weight of other functional ingredient(s) in addition to the antacid(s). In another embodiment, the delivery systems incorporate between about 0.01% and about 15% by weight of other functional ingredient(s) in addition to the antacid(s). In another embodiment, the delivery systems incorporate between about 0.01% and about 10% by weight of other functional ingredient(s). In a further embodiment, the delivery systems incorporate between about 0.01% and about 5% by weight of other functional ingredient(s).

4. Bioavailability Enhancers

The present invention also contemplates the inclusion of bioavailability enhancers in the delivery systems. Such compounds are known in the art and act to increase the absorption of functional ingredients by the body. Bioavailability enhancers can be natural or synthetic compounds. In accordance with the present invention, the bioavailability enhancer is a natural compound.

Natural bioavailability enhancers include ginger, caraway extracts, pepper extracts and chitosan. The active compounds in ginger include 6-gingerol and 6-shogoal. Caraway oil can also be used as a bioavailability enhancer (U.S. Patent Application 2003/022838). Piperine is a compound derived from pepper (*Piper nigrum* or *Piper longum*) that acts as a bioavailability enhancer (see U.S. Patent No. 5,744,161). Piperine is available commercially under the brand name Bioperine® (Sabinsa Corp., Piscataway, NJ).

One or more of the above-described bioavailability enhancers may be included in the delivery systems in order to enhance the bioavailability of the antacid(s) and/or other functional ingredients. Typically, one or more bioavailability enhancer can be included in the delivery system in an amount between about 0.02% to about 0.6% by weight.

PROCESS FOR PREPARING THE DELIVERY SYSTEM

In accordance with the present invention, the delivery systems remain flowable at temperatures below 100°C which allows for full dispersion and incorporation of the antacid(s) and other optional functional ingredients into the matrix while minimising or preventing degradation of these compounds. Thus, although the actual methodology used to prepare the delivery systems may vary depending on the individual components selected to make up the matrix, the process of preparing the matrix comprises the step of incorporating the antacid(s) and other optional functional ingredient(s) into the matrix at temperatures below 100°C. In one embodiment of the present invention, the process of preparing the matrix comprises the step of incorporating the functional ingredient(s) into the matrix at temperatures below about 75°C. In another embodiment, the process of preparing the matrix comprises the step of incorporating the functional ingredient(s) into the matrix at temperatures below about 65°C. In another embodiment, at least one functional ingredient is dispersed in the solvent component prior to admixture with the other matrix components.

Various standard methods known in the confectionery manufacturing industry can be used to prepare the delivery systems and selection of the appropriate method is considered to be within the ordinary skills of a worker in the art. Batch processes, such as kettle cooking, as well as continuous processes, such as direct steam injection jet cookers and indirect steam tubular heat exchangers, are suitable for preparing the delivery system.

The following description represents a general method of preparing a delivery system of the present invention.

Briefly, the process comprises the following steps: a blend of the hydrocolloid component and the sugar component, and optionally water, is prepared. A ratio of components is selected that will result in a final product with the desired moisture content (*i.e.* 10% – 40%). The hydrocolloid(s) may be pre-hydrated in water or may be hydrated during this blending step. The blend is heated to a temperature of less than 100°C, for example between 60°C and 80°C, such that all ingredients are incorporated. Alternatively, the sugar component, and optionally water, can be heated to a temperature of less than 100°C (for example between 60°C and 80°C) prior to

addition of the dry or pre-hydrated hydrocolloid(s) under shear. The temperature of the mixture is then reduced to between 50°C and 80°C. The antacids and/or other optional functional ingredient(s) are dispersed or dissolved in solvent at or below 70°C, for example below 50°C. If required, one or more sources of mono- or divalent cations and one or more pH adjusting agents can be added to either, or both, of the above preparations. The two preparations are then combined. Flavourings and colourings may optionally be added after this step.

As an alternative to adding pH adjusting agents as indicated above, the pH of the matrix can be adjusted, as necessary, after combining the two preparations. Suitable methods of adjusting the pH of food products are known in the art and include, for example, the addition of buffers, acids or bases, such as citric acid, sodium citrate, phosphates, sodium hydroxide, potassium hydroxide or a combination thereof.

As indicated above, the final product has a moisture level between 10% and 40%, for example between 15% and 20%, and a water activity of less than 0.9.

In one embodiment of the invention, the process includes the step of heating the blend of hydrocolloid(s) and the sugar component (and optionally water) to a temperature between about 60°C and about 70°C. In another embodiment, the process includes the step of heating the sugar component, and optionally water, to a temperature between about 60°C and about 70°C prior to addition, under shear, of the dry or pre-hydrated hydrocolloid(s). In a further embodiment, the process includes the step of dispersing or dissolving the antacids and/or other optional functional ingredient(s) in the solvent at a temperature between about 40°C and about 50°C.

Once the matrix has been prepared as described above, it can then be moulded, for example, using the standard Mogul process or by injection-filling of pre-formed moulds. One skilled in the art will appreciate that the matrix can also be readily adapted to extrusion methods.

In final form, the delivery systems of the present invention are semi-solid, intermediate moisture systems, having some properties clearly identified with those of jellies and some properties that are similar to the jujube variety of confectioneries.

The matrix of the delivery systems is thus formulated to be semi-solid at normal room temperature (*i.e.* at temperatures between about 20°C and about 30°C). It will be readily apparent that depending on the particular components selected for use in the preparation of the matrix, the amount of each to be included in the matrix may need to be manipulated within the ranges indicated in order to achieve a semi-solid, intermediate moisture product. One skilled in the art of confectionery design can readily determine which component(s) will need to be adjusted in order to achieve an end-product with these physical properties.

Similarly, it will be readily apparent to one skilled in the art that variations can be made to the described process dependent on the type and the actual amount of each component used (within the given ranges) in order to obtain an end product with the described properties. For example, if the hydrocolloid comprises a starch, it is known in the art that the gelatinisation temperature of the starch may be affected when certain sugars and sugar alcohols are used. If required, therefore, the starch and the sugar component can be heated above 100°C to allow full gelatinisation of the starch to occur and the desired moisture content to be reached. The temperature of the mixture can then be reduced to between 50°C and 80°C prior to addition of the functional ingredient(s) and optionally flavourings and colourings.

As is known in the art, modified celluloses, such as methylcellulose and hydroxypropyl methylcellulose, have unique properties resulting in the ability to delay hydration of these carbohydrates during preparation processes. Thus, when these compounds are used a "delayed hydration technique" may be employed in which the modified cellulose is first dispersed in the solvent component of the matrix and then mixed with the other components in aqueous solution. The hydration of the modified cellulose then takes place gradually as the processing is complete and the moulded matrix cools. Delayed hydration and non-aqueous fluid carrier techniques using modified celluloses are standard in the art.

Similarly, the choice of hydrocolloid can affect the set up temperature of the matrix. The use of a combination of starch, gelatine and gellan, for example, can provide a matrix set-up temperature of about 35°C, as can a combination of starch, gelatine and

pectin. In contrast, the use of other hydrocolloids or combinations of other hydrocolloids with or without gelatine or gellan, may alter the set up temperature of the matrix. For example, the use of starch in combination with locust bean gum or carageenan often results in set up temperatures of around 60°C. The choice of hydrocolloid is thus dependent on the functional ingredient(s) to be incorporated into the matrix. Temperature sensitive functional ingredients will require a hydrocolloid or hydrocolloid mixture that provides a low set up temperature (such as the gelatine:gellan and gelatine:pectin mixtures described above), whereas other hydrocolloids or mixtures thereof can be used with functional ingredients that can tolerate higher temperatures.

The manner in which the individual components are combined may also be varied although typically at least one of the functional ingredients is dispersed in solvent prior to addition to the remainder of the components. For example, the sugar component may be heated with the water and salts prior to addition of the hydrocolloid(s). Similarly, when two or more hydrocolloids are being used, they do not have to be added to the mixture at the same time. One hydrocolloid and part of the sugar component could be mixed and heated prior to being blended with the other hydrocolloid and remainder of the sugar component. Alternatively, one hydrocolloid and the sugar component could be mixed and heated prior to addition of the second hydrated hydrocolloid, or one hydrocolloid may be added to the solvent component and then blended with the second hydrocolloid and sugar component. These and other variations are considered to be within the scope of the present invention.

TESTING THE DELIVERY SYSTEM

1. Physical Properties

One skilled in the art will appreciate that molecular interaction between one or more of the functional ingredient and the matrix may affect the physical attributes of the final product. As is standard in the art, therefore, a sample of the delivery system incorporating the antacid(s) and optionally other functional ingredient(s) can be prepared prior to large-scale production and tested in order to determine whether the matrix retains the desired physical properties, *i.e.* substantially uniform dispersion of

the antacid(s) and other functional ingredients, less than 20% degradation of these compounds during the preparation of the matrix and water activity less than 0.9.

For example, dispersion of the antacid(s) in the final delivery system can be determined by dividing a single unit of the delivery system into several subunits and analysing the content of antacid in each subunit, for example as a % by weight. The levels of antacid can readily be measured by standard analytical techniques such as mass spectrometry, UV or IR spectrometry, or chromatographic techniques, such as gas chromatography or high-performance liquid chromatography (HPLC). If the % by weight of antacid in each subunit is similar, then the antacid is said to be substantially uniformly dispersed throughout the product. One skilled in the art will appreciate that the % by weight need not be identical for each subunit to indicate substantially uniform dispersion. In accordance with the present invention, the % by weight of antacid for each subunit of the final delivery system varies by less than 2%. In one embodiment, the % by weight of antacid for each subunit of the final delivery system varies by less than 1.5%. In other embodiments, the % by weight of antacid for each subunit varies by less than 1% and by less than 0.5%.

The dispersion of other functional ingredients incorporated into the delivery system can also be measured as described above.

Similarly, the degradation of the functional ingredient(s) can be determined by standard analytical techniques taking into account the total amount of each compound included in the preparation of the matrix. Many functional ingredients degrade to yield specific breakdown products, the presence or absence of which can be determined in the final product using standard techniques, such as spectrophotometric and chromatographic techniques, *e.g.* gas chromatography and HPLC. As indicated above, the degradation of the functional ingredients is minimised during the preparation of the delivery system and is less than about 20% in the final product.

The water activity (a_w) of the final product can also be analysed by standard techniques. The a_w of a food product is a physical property that has direct implications on the microbial safety of the product and influences storage stability. Lower a_w values generally indicate a food product that is more stable and more resistant to

microbial contamination than one with a high a_w value due to the requirement for water of most microbes and the fact that most deteriorative processes in food products are mediated by water. As is known in the art, the a_w value of a food product is the ratio of the water vapour pressure of the product (p) to that of pure water (p_o) at the same temperature, *i.e.* $a_w = p/p_o$. In accordance with the present invention, the water activity of the final delivery system is less than about 0.9, for example between about 0.5 and about 0.7.

Other parameters, such as the release rate of the functional ingredients from a delivery system can also be tested by standard methods (for example, the USP Basket Method or Paddle Method; see U.S. Pharmacopoeia XXII (1990)). Typically, a sample of the delivery system containing a known amount of functional ingredient(s) (for example, a unit dose) is placed in an aqueous solution of a predetermined pH, for example around pH 1.2 to simulate stomach conditions and/or around pH 7.4 to simulate colon conditions. The suspension may or may not be stirred. Samples of the aqueous solution are removed at predetermined time intervals and are assayed for their content of functional ingredients by standard analytical techniques, such as those indicated above.

In addition, the delivery system may undergo testing to evaluate such factors as the microbial content of the product and the shelf-life of the product. Such quality control testing is standard in the art and can be conducted using known methods.

For example, microbial analysis of the delivery system can be conducted using techniques approved by the appropriate regulatory board, such as those described in "The Compendium of Analytical Methods: HPB Methods for the Microbiological Analysis of Foods" issued by the Health Products and Food Branch of Health Canada. Shelf life is typically evaluated using accelerated shelf life tests in which the stability of the system and the degradation of the functional ingredients contained therein is analysed under conditions that are known to accelerate the degradation of food products and can be correlated to the stability of the product under normal storage conditions.

Texture measurements can also be made to determine whether the delivery system has the required gel strength/hardness. Gel strength or hardness can be measured either directly (expressed as grams force) and indirectly (expressed as a viscosity), or both.

Methods of measuring gel hardness are known in the art. For example, a Kramer single blade shear cell can be used. In this test, a shear blade is driven down at a constant speed through a sample of the delivery system and the peak force as the blade cuts through the sample is measured. The test force is typically reported in kilograms-force. Various machines are available to conduct such testing, for example, a Universal Testing machine such as that available from Instron or Stable Micro Systems (*e.g.* the Model TA.HD Texture Analyzer).

Gel hardness can also be measured using a standard Brookfield viscometer (*e.g.* the Model RVDV), which measures the force required to cut through a gelled liquid. A spindle rotating at a set speed is slowly lowered into a sample of the delivery system and the torque required for the spindle to "cut" through the sample is measured. Temperature is important to obtain an accurate viscosity reading and thus the samples are usually tempered to 21°C to 24°C prior to testing. The cutting force or torque reading on the viscometer is an empirical measure of gel strength and is reported in centipoise (cps).

Another method useful for measuring sensory texture utilises the Hamann Torsion/Vane Gelometer. This system provides fracture shear stress and shear strain values and real time test graphs of stress *vs.* strain or angular deformation. Stress (strength) and strain (deformability) are not "geometrically coupled" as in most traditional (empirical) textural tests, therefore, the strain measurement remains unaffected by the magnitude of the stress measurement. Strain has been found to be the best indicator of gelling quality for proteins and hydrocolloids, as this parameter is less sensitive to concentration effects, and is also a good indicator of the perceived "rubberiness" of food gels. Strain values also predict machining characteristics of food gels, such as ease of slicing. Furthermore, the sample shape does not change during testing with the Torsion Gelometer, thus minimal fluids will be forced from the sample during testing and the gel itself is tested rather than a dehydrated derivative.

The mode of failure in torsion testing yields important information about the texture of the sample. Test samples of the delivery system are formed in either cylindrical moulds (tubes) for subsequent milling, which eliminates surface skin effects, or in a dumbbell old. Samples are then cut to a standard length (for example, 1 inch) and loaded into the measuring cell for testing. Data collection continues for a time past the breaking of the sample (peak stress or Fracture Point). Stress (in kPa), strain, rigidity modulus (G = stress/strain) and slope ratio at failure can be measured in this method

Palatability can also be tested using standard techniques. Methods of evaluating the organoleptic properties of foods are well-known in the art. For example, sensory evaluations can be performed using individuals who are spatially separated from each other, for example, in individual partitioned booths, as testers and a hedonic nine-point scale that ranges from 1 (most disliked) to 9 (most liked), with 5 indicating no preference [Larmond, *Laboratory methods for Sensory Evaluation of Foods,* Research Branch of Agriculture Canada (1977)]. Odour and taste are generally evaluated under a red light, which masks any differences in the colour of the product. Another nine-point hedonic scale test can be carried out under normal light to evaluate the acceptability of the appearance of the product.

2. Efficacy

The delivery systems of the present invention can be tested for efficacy *in vivo*. Typically, the efficacy is tested by conducting bioavailability studies using standard techniques in the pharmaceutical art, such as peak plasma levels and pharmokinetic analyses (see, for example, Enna, *et al., Current Protocols in Pharmacology,* J. Wiley & Sons, New York, NY).

Antacids can be assessed *in vivo* qualitatively by means of pH-meter studies in healthy volunteers, under both baseline conditions and during secretory stimulation as is known in the art.

Alternatively, antacids may be evaluated *in vitro* on the basis of acid neutralising capacity, *i.e.* the total amount of acid neutralised. For example, if desired, the delivery systems can be tested for their acid neutralising capacity following the procedure set

out in the U.S. Pharmacopeia 23/National Formulary 18. Acid neutralising capacity can also be measured using automatic titration methods in which the antacid product is added to distilled water and sufficient acid is added to maintain the pH at a predetermined value. The kinetics of the neutralisation process can be studied *in vitro* using the Rossett-Rice test. In this test, antacid is added to 100 ml of 0.07 N HCl and the pH is continuously monitored. 0.1 N HCl is pumped into the reaction vessel at a rate of 4 mL/min to simulate the secretion of acid into the stomach. The plot of pH vs. time allows for the determination of the time required for pH to reach 3.0 (the lag time) and the maximum pH achieved. The Rossett-Rice time is defined as the time that the pH is maintained between the level of pH 3-5 and is an indicator of antacid effectiveness.

Newer dynamic methods can also be used. These methods are based on a computer-controlled artificial stomach-duodenum model, which simulates flux and pH conditions in the gastroduodenal tract, taking into account interactions with the gastric mucosa. The model thus reproduces the *in vivo* medium encountered by antacids and is capable of reflecting the effect of antacids on gastric pH as well as the antacids' resistance to acidification. A good correlation has been demonstrated between this method and human *in vivo* studies for several antacids.

FORMAT OF THE DELIVERY SYSTEM

The present invention contemplates various formats for the delivery systems. For example, the delivery systems may be in the form of a confectionery, such as a jujube, in which case it may be formulated alone or it may further comprise a coating, such as a chocolate or yoghurt coating. Preparation of jujube or jelly type confectionery products are known in the art and include, for example, the use of moulds, injection-filling of pre-formed packages and extrusion processes. It will be readily apparent to one skilled in the art that such standard techniques can be applied to prepare a wide variety of different shaped confectioneries.

The present invention further contemplates the delivery system as a filling or a coating, for example, for baked goods such as wafers or cookies. For example, the

matrix can be used as a layer between two wafers, or a jelly layer on the top of a cookie or sponge, in which case the product may be further coated with a chocolate or other flavoured coating, if desired, as described above for confectionery products. Alternatively, the matrix may be used to fill doughnut type baked goods. Methods of filling and coating baked goods are also well known in the art.

ADMINISTRATION AND USE

The antacid(s) and the other optional functional ingredients are incorporated into the delivery system at levels sufficient to affect the structure or function of the body when taken regularly. Such levels are known in the art (see, for example, *Physician's Desk Reference,* 57th Edition, 2003).

Representative daily oral doses for an adult human for some common antacids are provided in Table 2.

Table 2: Adult Dosage Ranges for Representative Antacids

Name	*Common Dosage Range (mg)*	
Aluminium hydroxide	80	650
Bismuth subsalicylate	262	525
Calcium carbonate	300	1000
Magnesium carbonate	40	358
Magnesium hydroxide	165	400
Magnesium trisilicate	20	40

Various combinations of antacids are suitable for incorporation into the delivery systems. Exemplary, non-limiting combinations are provided in Table 3.

Table 3: Exemplary Combinations of Antacids

Antacid	*Possible Combinations*

Antacid	*Possible Combinations*
Alumina	in combination with: - calcium carbonate and magnesia - magnesia - magnesium carbonate - magnesium carbonate and magnesium oxide - magnesium trisilicate - magnesium trisilicate and magnesia - magnesium trisilicate and sodium bicarbonate
Aluminium hydroxide	in combination with: - calcium carbonate and magnesium carbonate - calcium carbonate and magnesium trisilicate - magnesium hydroxide - magnesium trisilicate - magnesium hydroxide and magnesium aluminium silicate
Calcium carbonate	in combination with: - aluminium hydroxide - aluminium hydroxide and magnesium hydroxide - magnesia - magnesium trisilicate - magnesium carbonate - magnesium carbonate and bismuth subnitrate - magnesium carbonate and magnesium oxide - sodium bicarbonate and potassium bicarbonate
Magnesium carbonate	in combination with: - sodium bicarbonate - aluminium hydroxide and sodium bicarbonate
Magnesium trisilicate	in combination with: - alumina and magnesia
Sodium bicarbonate	in combination with: - calcium carbonate and potassium bicarbonate - sodium citrate

Antacid	*Possible Combinations*
	- sodium citrate and potassium bicarbonate
Sodium tartrate	in combination with: - sodium citrate

The antacid delivery system of the present invention can be administrated to a subject to help neutralise excess stomach acid, *i.e.* decrease excess stomach acidity, and thereby relieve or alleviate symptoms associated with hyperacidity; acid indigestion; sour stomach; gastritis; heartburn, including heartburn due to hiatus hernia and during pregnancy; pyrosis; dyspepsia; gastritis; oesophagitis; gastroesophageal reflux (including acid reflux and reflux oesophagitis); peptic ulcer and duodenal ulcer.

Specific combinations of functional ingredients can be included in the delivery systems in order to provide relief from a particular set of symptoms in a subject. The following represent exemplary, non-limiting examples of suitable combinations of functional ingredients.

For example, delivery systems comprising a combination of one or more antacids with dimethicone can be useful in treating indigestion with associated bloating or flatulence, meteorism and post operative gas pain. Some exemplary, non-limiting combinations include, alumina, magnesia and simethicone; calcium carbonate and simethicone; calcium carbonate, magnesia and simethicone; magaldrate and simethicone, and simethicone, alumina, calcium carbonate and magnesia. Other combinations are known in the art to be effective and can be used in the delivery systems of the present invention. Antacid and activated charcoal combinations are also suitable for this application.

For the relief and alleviation from symptoms associated with peptic and duodenal ulcers, hyperacidity, dyspepsia, gastritis or oesophagitis, delivery systems can be formulated that comprise, for example, one or more antacids in combination with famotidine, with oxethazaine, with sucralfate, or with DGL. Such delivery systems may further comprise a rafting agent. Delivery systems comprising one or more antacids in combination with other H_2 blockers, and/or local anaesthetics can also be

formulated for subjects suffering from peptic and duodenal ulcers, hyperacidity, dyspepsia, gastritis or oesophagitis.

For the relief and alleviation from symptoms associated with gastroesophageal reflux, heartburn and/or oesophagitis, delivery systems can be formulated that comprise, for example, one or more antacids in combination with alginic acid or sodium alginate. The use of bicarbonate antacids with rafting agents has been shown to help in the formation of a foam from the gel precipitate formed by the alginate, due to the conversion of bicarbonate by gastric acid into carbon dioxide that gets trapped in the gel precipitate. Delivery systems comprising rafting agents, therefore, can include a bicarbonate antacid in order to help the action of the rafting agent. Delivery systems comprising one or more antacids in combination with a H_2 blocker, with a proton pump inhibitor, and/or with metaclopramide are also useful for subjects suffering from gastroesophageal reflux.

It is also contemplated that, when the delivery system comprises calcium and/or magnesium salts as one or more of the antacids, the delivery system can function as a mineral supplement. The present invention further contemplates that "dual-purpose" antacid delivery systems can be designed that comprise a combination of functional ingredients, the main component of which is one or more antacids. The remaining functional ingredients of the combination being selected to produce a specific physiological effect. Non-limiting examples of such effects include the improvement of an individual's health or well-being, energy levels, weight maintenance, and the like, as described above, as well as those effects outlined in Table 1.

As a specific example, the antacid delivery systems of the present invention can be used as a supplement for sports nutrition purposes. Sports nutrition is associated with the intake of functional ingredients that affect various factors relating to an individual's endurance, performance, recovery, energy levels, weight maintenance, and the like. Many athletes experience heartburn and/or acid reflux after exercise and can benefit from an easily ingestible antacid. In addition, the intake of certain antacids, such as sodium bicarbonate, prior to exercise has been associated with a delay the onset of muscle fatigue and thus increased performance in high-intensity

exercise, such as sprinting and weight lifting. The delivery systems of the present invention can thus be used prophylactically to help delay muscle fatigue associated with, and/or to decrease recovery time after, high-intensity exercise. In this context, the antacid delivery systems can be designed to include other functional ingredients intended to increase endurance, improve performance and/or reduce recovery time.

The delivery systems of the invention can be formulated in various unit sizes depending on the amount of antacids(s) (and other optional functional ingredients) to be incorporated therein and on the requirements of the target consumer. For example, smaller units may be required for children and animals than for adult humans. The delivery systems of the present invention can be formulated to have a unit size between about 3 grams and about 30 grams. In one embodiment, a unit of the delivery system is between about 3 and about 20g. In another embodiment, a unit of the delivery system is between about 3 and about 15g. In another embodiment, a unit of the delivery system is between about 3 and about 10g. Where appropriate, the delivery systems can be provided in a multi-dose format that is pre-scored into unit doses.

It is understood that the total daily intake of antacid(s) may be based on administration of one unit of the delivery system, or it may be based on administration of more than one unit. The amount of antacid(s) in a single unit will thus vary depending on the size of the units and the number to be administered daily.

The delivery systems can be formulated for administration to humans or other animals. For administration to humans, flavours and formats that appeal to the particular group of consumers being targeted can be employed. For example, delivery systems that are formulated with confectionery-like qualities and flavours are appealing to children who are often resistant to taking medications or supplements due to unpleasant tastes or mouthfeel.

Similarly, the delivery systems can be formulated for administration to a non-human animal using flavours that more typically appeal to non-human animals, for example, fish, poultry or meat flavours. Administration of functional ingredients to an animal in conventional solid dosage forms, such as tablets and capsules, can be problematic in

that the animal often expels them, and multiple dosing is often difficult because the animal learns to resist the dosing procedure. It will be readily apparent that the delivery system of the present invention, which is formulated as a foodstuff, is ideally suited for administration of antacids to animals.

KITS

The present invention additionally provides for kits containing a delivery system for administration to a human or non-human animal. The kit would provide an appropriate dosing regimen over a prescribed period for the antacid(s) and other functional ingredient(s) contained in the delivery system.

The kits of the invention comprise one or more packages containing the delivery system and may further comprise a set of instructions, generally written instructions, relating to the use and dosage of the antacid(s) and other optional functional ingredient(s) contained in the delivery system. The instructions typically include information as to the appropriate dosage and dosing schedule for the functional ingredients in terms of units of the delivery system. The packages containing the delivery system may in the form of unit doses, bulk packages (for example, multi-dose packages) or sub-unit doses. The doses may be packaged in a format such that each dose is associated, for example, with a day of the week. There may also be associated with the kit a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of biological products, which notice reflects approval by the agency of manufacture, use or sale for human or animal administration.

To gain a better understanding of the invention described herein, the following examples are set forth. It should be understood that these examples are for illustrative purposes only. Therefore, they should not limit the scope of this invention in any way. All percentages throughout the specification and claims are by weight of the final delivery system unless otherwise indicated.

EXAMPLES

EXAMPLE 1: Antacid Delivery Systems

The delivery systems described below are formulated to have a final pH between 6.0 and 9.0, more typically between 7.0 and 9.0. The delivery systems have a final a_w between about 0.5 and about 0.65.

1.1 Delivery System for Antacids #1

Ingredient	*% by Weight*
Glycerol	47.65%
Propylene glycol	1.15%
Calcium carbonate	15.63%
63 DE Corn syrup	8.02%
High Fructose Corn Syrup	9.41%
Gelatine	4.56%
Pectin	0.25%
Sweetening agents	0.06%
Modified Starch	1.53%
Flavour	0.08%
Colour	0.29%
Water	11.37%
TOTAL	100.00%

The product was formulated to deliver 750 mg of calcium carbonate in 4.8g dose. The moisture content of final delivery system was approximately 16% by weight.

1.2 Delivery System for Antacids #2

Ingredient	*% by Weight*
Glycerol	45.23%
Propylene glycol	2.18%
Calcium carbonate	8.34%
Magnesium Hydroxide	6.67%
Aluminium Hydroxide	6.67%

63 DE Corn syrup	5.08%
High Fructose Corn Syrup	5.96%
Gelatine	4.06%
Pectin	0.25%
Sweetening agents	0.05%
Modified Starch	1.69%
Flavour	0.20%
Colour	0.29%
Water	13.33%
TOTAL	100.00%

The product was formulated to deliver 500 mg of calcium carbonate and 400mg each of aluminium and magnesium hydroxide in a 6g dose. The moisture content of final delivery system was approximately 16% by weight.

1.3 Delivery System for an Antacid with Antiflatulent

Ingredient	*% by Weight*
Glycerol	44.62%
Propylene glycol	1.63%
Calcium carbonate	16.67%
Simethicone	0.83%
63 DE Corn syrup	6.89%
High Fructose Corn Syrup	8.09%
Gelatine	5.13%
Pectin	0.25%
Sweetening agents	0.05%
Modified Starch	1.71%
Flavour	0.15%
Colour	0.29%
Water	13.69%
TOTAL	100.00%

The product was formulated to deliver 1000 mg of calcium carbonate and an effective level of the antigas ingredient Simethicone in a 6g dose. The moisture content of final delivery system was approximately 16% by weight.

1.4 Delivery system for Antacids #3

Ingredient	*% by Weight*
Glycerol	39.96%
Propylene glycol	1.31%
Calcium carbonate	11.50%
Magnesium Hydroxide	9.25%
Aluminium Hydroxide	9.25%
63 DE Corn syrup	4.62%
High Fructose Corn Syrup	5.42%
Gelatine	3.90%
Pectin	0.25%
Sweetening agents	0.05%
Modified Starch	1.00%
Flavour	0.20%
Colour	0.29%
Water	13.00%
TOTAL	100.00%

The product was formulated to deliver 500 mg of calcium carbonate and 400mg each of aluminium and magnesium hydroxide in a 4.35g dose. The moisture content of final delivery system was approximately 16% by weight.

The above antacid formulations were prepared by the following general method:

The glycerol and propylene glycol were blended and the antacids dispersed therein and the blend warmed to 40-50°C. The sugar syrups were blended with the water and warmed to 60-70°C. The gelatine, pectin, sweetening agents and other dry ingredients were preblended and introduced into the syrup under shear. The antacids blend was then uniformly blended with the gelatine preparation. Flavour and colour were then added and the whole maintained between 40°C and 55°C.

EXAMPLE 2: Delivery Systems using Other Functional Ingredients

The following delivery systems (formulated using functional ingredients other than antacids) demonstrate how the components of the matrix can be varied. These systems can be readily adapted for antacid delivery by a worker skilled in the art, by replacing the listed functional ingredients with one or more antacids and optionally, one or more other functional ingredient, in accordance with the present invention. A worker skilled in the art will recognise that the use of pH modifying or buffering ingredients included when formulating with specific functional ingredients may not be required when adapting the formulations to deliver antacids. The moisture content of the following delivery systems was between about 13% and about 17% by weight.

2.1 Ingredient	*% by Weight*
Glycerol	14.57%
Propylene Glycol	5.30%
Functional ingredients*	13.38%
Corn Syrup 62DE	31.79%
Sucralose	0.04%
Modified Starch	2.65%
Potassium citrate	2.15%
High fructose corn syrup	9.27%
Water	14.57%
Gelatine 100 bloom type B	1.32%
Gelatine 250 bloom type A	3.97%
Gellan (Kelcogel® LT100) CP Kelco	0.32%
Colour	0.21%
Flavour	0.45%
Total:	**100.00%**

* creatine monohydrate (11.71%) and dimethylglycine (1.67%)

2.2 *Ingredient*	*% by Weight*
Glycerol	12.57%
Propylene Glycol	4.19%
Functional ingredient (arginine)	14.02%
Maltitol solution	33.52%
Modified Starch	2.79%
Potassium citrate	1.17%
Sucralose	0.04%
High fructose corn syrup	9.78%
Water	15.37%
Gelatine 250 bloom type A	5.59%
Gellan (Kelcogel® LT100) CP Kelco	0.28%
Colour	0.168%
Flavour	0.503%
Total:	**100.00%**

2.3 *Ingredient*	*% by Weight*
Glycerol	13.82%
Propylene Glycol	5.53%
Functional ingredients*	11.02%
Isomalt syrup	33.17%
Sucralose	0.055%
Modified Starch	2.76%
Potassium citrate	2.24%
High Fructose Corn syrup	9.68%
Water	15.20%
Gelatine 250 bloom type A	5.53%
Gellan (Kelcogel® LT100) CP	0.33%
Colour	0.08%

Flavour	0.08%
Total:	**100.00%**

*creatine monohydrate (4.59%), conjugated linoleic acid (CLA; 4.59%), lecithin (1.05%), N,N, dimethylglycine (0.47%), rhodiola / seabuckthorn extract solution (0.21%) and chromium chelate (0.11%).

2.4 Ingredient	*% by Weight*
Glycerol	14.82%
Propylene Glycol	5.39%
Functional ingredient (creatine monohydrate)	11.91%
Corn Syrup 62DE	32.33%
Sucralose	0.04%
Modified Starch	2.70%
Potassium citrate	2.19%
High fructose corn syrup	9.43%
Water	14.82%
Gelatine 100 bloom type B	1.34%
Gelatine 250 bloom type A	4.04%
Gellan (Kelcogel® LT100) CP Kelco	0.33%
Colour	0.21%
Flavour	0.46%
Total:	**100.00%**

The above formulations were prepared by the following general method:

Glycerol and propylene glycol were first blended and at least one functional ingredient was added. The blend was heated to 65–70°C. In a separate container, gelatine and gellan were blended together. The fructose syrup and water were mixed and heated to 60°C, after which the gelatine:gellan mixture was added with constant agitation. The mixture was then heated to 75°C to allow the components to dissolve. In a third container, the syrup was warmed to 30–35°C and the sucralose, potassium citrate, other functional

ingredients and starch were then blended in. The syrup mixture was combined with the gelatine:gellan mixture and heated to 75–80°C until the moisture content was reduced and the desired solids level achieved. The glycerol mixture was then added together with the colour and flavour additives. The delivery system was then moulded using standard techniques.

2.5

Ingredient	*% by Weight*
Glycerol	27.9990%
Propylene Glycol	3.4145%
Potassium Hydroxide	0.1208%
Functional ingredient (creatine monohydrate)	24.0154%
High Fructose Corn Syrup	15.7068%
Corn syrup	14.7962%
Modified Starch	2.5040%
Water	3.9836%
Potassium phosphate	0.4234%
Sucralose	0.0381%
Potassium citrate	0.9526%
Gelatine Type A	4.7803%
Pectin	0.2732%
Flavour	0.5464%
Colour	0.2982%
Total:	**100.0000%**

The following method was used to prepare the above delivery system. Glycerol and propylene glycol were first blended and the creatine was added. The blend was heated to 45-50°C. In a separate container, the gelatine, pectin, starch and sucralose were blended together. The fructose and glucose syrups and water were mixed and heated to 60°C, after which the salts and pH modifying agents were added with constant agitation and heated to 60-70°C to dissolve the solids. The powder blend was then incorporated into the syrup mixture using high shear. Finally, the creatine mixture was added, together with the

colour and flavour additives, and blended. The delivery system was then moulded using standard techniques.

2.6 Ingredient	*% by Weight*
Glycerol	16.67%
Propylene Glycol	7.86%
Functional ingredients*	9.36%
Maltitol syrup	35.86%
High fructose corn syrup	15.73%
Sucralose	0.06%
Modified Starch	3.15%
Potassium citrate	1.42%
Potassium hydroxide	0.92%
Water	1.38%
Gelatine	6.29%
Pectin	0.31%
Colour	0.3%
Flavour	0.74%
Total:	**100.00%**

*Conjugated linoleic acid (Clarinol 80; 7.86%), citrus aurantium (0.5%), inulin (0.63%), caffeine (0.25%), mixed tocopherols (0.04%) and ascorbic acid (0.03%).

The following method was used to prepare the above delivery system. The glycerol and propylene glycol were first blended together. At least one functional ingredient was then added and the resultant mixture was warmed to 60–70°C. In another container, the syrups, water, potassium citrate and potassium hydroxide were combined and warmed to 60–70°C. The starch, gelatine, pectin, sucralose and remaining functional ingredients were pre-blended then added to the syrup mixture under high shear. This mixture was combined with the glycerol mixture and the temperature maintained at 60–70°C until the moisture content was reduced

sufficiently to give the desired solids level. Colour and flavour were added and the mixture was then moulded using standard techniques.

2.7 *Ingredient*	*% by Weight*
Glycerol	15.97%
Propylene Glycol	5.51%
Functional ingredient (creatine monohydrate)	16.71%
63 DE Corn syrup	21.20%
High Fructose Corn Syrup	24.78%
Gelatine 250 Bloom Type A	5.51%
Gellan	0.33%
Sucralose	0.06%
potassium citrate	1.40%
Modified Starch	2.75%
Water	4.96%
Flavour	0.56%
Colour	0.28%
Total:	**100.00%**

The following method was used to prepare the above delivery system. Creatine was added to a mixture of glycerol and propylene glycol, and heated to 40-60°C. The syrups were blended with water and the dry ingredients were mixed into the syrup mixture. The combined mixture was then heated to at least 80°C. Alternatively, the blended dry ingredients can be blended in with simultaneous live steam injection to reach at least 80°C. The solid content was then adjusted by addition of water if necessary to provide a final moisture content of between about 10% to about 30%. At this point, the temperature of the syrup mixture was lowered to between 50°C and 80°C and the glycerol-glycol mixture was added. Colour and/or flavouring additives were then added and the delivery system was injection filled into the preformed packaging.

2.8

Ingredient	*% by Weight*
Glycerol	27.96%
Propylene glycol	3.44%
Potassium hydroxide (45%)	0.30%
Functional ingredient (creatine monohydrate)	24.07%
Corn syrup 63DE	13.34%
High fructose corn syrup	15.65%
Water	6.30%
Potassium phosphate	0.43%
Potassium citrate	0.96%
Sucralose	0.03%
Gelatine	7.11%
Flavour	0.14%
Colour	0.27%
Total:	**100.00%**

2.9

Ingredient	*% by Weight*
Glycerol	26.32%
Propylene glycol	3.43%
Potassium hydroxide (45%)	0.23%
Functional ingredient (creatine monohydrate)	24.03%
Corn syrup 63DE	14.24%
High fructose corn syrup	16.72%
Water	4.04%
Potassium phosphate	0.43%
Potassium citrate	0.96%
Sucralose	0.04%
Gelatine	9.15%
Flavour	0.14%

Colour	0.27%
Total:	**100.00%**

The delivery systems of Examples 2.8 and 2.9 were prepared as follows. Glycerol and propylene glycol were first blended and the creatine was added. The blend was heated to 45-50°C. The syrups, water, salts and pH modifying agents were mixed and heated to 60-70°C with constant agitation to dissolve the solids. The gelatine and Sucralose were then incorporated into the syrup mixture using high shear and the temperature was reduced to approximately 50-60°C. Finally, the creatine mixture was added, together with the colour and flavour additives, and blended. The delivery system was moulded using standard techniques.

2.10 ***Ingredient***	***% by Weight***
Glycerol	30.19%
Propylene glycol	2.09%
Functional ingredient	3.33%
Bioavailability Enhancer (Gelucire 44/14)	3.33%
63 DE Corn syrup	19.24%
High Fructose Corn Syrup	22.56%
Gelatine	8.58%
Pectin	0.31%
KOH	0.26%
Sweetening agents	0.12%
Modified Starch	1.92%
Flavour	0.18%
Colour	0.35%
Water	7.53%
Total:	**100.00%**

The above formulations comprising a bioavailability enhancer was prepared as follows. The glycerol and propylene glycol were blended and the functional ingredient dispersed therein and the blend warmed to 40-55°C. The sugar syrups were

blended with the water and warmed to 60-70°C. The gelatine, pectin, sweetening agents and other dry ingredients were preblended and introduced into the syrup under shear. The functional ingredient blend was then uniformly blended with the gelatine preparation. Flavour and colour were then added and the whole maintained between 40°C and 55°C.

2.11

Ingredient	*% by Weight*
Glycerol	33.0 - 43.0%
High fructose corn syrup	13.0 - 19.0%
63 DE corn syrup	11.0 - 16.0%
Water	8.0 - 12.0%
Gelatine	5.0 - 7.0%
Functional ingredient #1*	3.5 - 6.5%
Functional ingredient #2§	3.0 - 5.0%
Propylene Glycol	2.0 - 3.0%
Modified starch	1.5 - 3.0%
Caffeine	1.0 - 2.0%
Methylcellulose	0.8 - 2.0%
Flavour	0.5 - 3.0%
Colour	0.01 - 1.0%
Pectin	0.01 - 0.3%
Artificial sweetener	0.01 - 0.2%
Vitamin D	0.005 - 0.1%
Citric acid	0.0 - 0.5%

* calcium carbonate

§ Blend of carnitine, ginseng, green tea, taurine, tyrosine and yerbamate

The above formulation was prepared by the following process. The glycerol and propylene glycol were blended. The calcium, methylcellulose and proprietary blend of actives are preblended together then incorporated into the glycerol/propylene glycol and the blend warmed to 40-50°C. When the vitamin D is used in powder form it can be added to the preblend, when used in liquid form, it can be added to the glycerol /propylene glycol prior to adding the dry preblend. The caffeine was dissolved in

water heated to between 65°C and 85°C. The sugar syrups were then incorporated and the temperature adjusted to 60-70°C. The gelatine, pectin, starch and sweetening agents were preblended and introduced into the syrup(s) under shear. The calcium blend was then uniformly blended with the gelatine preparation. Flavour and colour were then added and the whole maintained between 40°C and 55°C.

EXAMPLE 3: Accelerated Shelf-Life Determination

An accelerated shelf life test was conducted on the creatine delivery system prepared by the method described in Example 2.6. Microbial analysis was conducted using approved methods as described in The Compendium of Analytical Methods: HPB Methods for the Microbiological Analysis of Foods (Volume 2) issued by the Health Products and Food Branch of Health Canada. After subjecting samples of the delivery system to a temperature of 35°C and a relative humidity of 45-55% for a period of 35 days, the samples were tested for the presence of various microorganisms as listed in Table 4. The average water activity of the samples tested was approximately 0.51.

The results, as shown in Table 4, indicate that after a period of 35 days at the above-described conditions, microbial contamination was minimal and well below accepted levels. Based on these results, the delivery system is shown to have a stable shelf life of at least one year from the date of manufacture.

In addition to the above microbial analysis, the creatine level in each sample was determined by HPLC prior to the test and after 35 days. The average creatine content for four samples randomly selected for analysis after 35 days was compared to the average creatine content for three samples taken prior to the shelf life test. The results indicated that levels of creatine monohydrate remained stable in the jujubes after 35 days exposure to the above-described conditions. Prior to the start of the experiment, three jujubes had an average of 13.4% by weight of creatine monohydrate. After 35 days, four jujubes were shown to have an average of 14.2% by weight of creatine monohydrate, which is within the error limits of the analysis performed.

Table 4: Microbial Analysis of a Creatine Delivery System – Accelerated Shelf Life Determination

Water activity: approximately 0.51
Time: 35 days
Temperature: 35°C
Humidity: 45-55%

TEST CONDUCTED	*HPB REFERENCE NUMBER*	*RESULTS (No. Colonies/gm product)*
Total aerobic plate count	MFHPB – 18	< 10
Total coliforms	MFHPB – 34	< 10
E. coli	MFHPB – 34	< 10
Yeast	MFHPB – 22	< 50
Mould	MFHPB – 22	< 50
Yeast Osmophilic	MFHPB – 22	< 50
Mould Osmophilic	MFHPB – 22	< 50
Staphylococcus aureus	MFHPB – 21	< 25
Salmonella	MFHPB – 20	not detected

EXAMPLE 4: Analysis of Water Activity of the Delivery System

Water activity was measured in samples of the delivery system that had been prepared according to the method described in Example 2.6.

The procedure for measuring water activity is based on the fact that the water activity of a sample is equal to the relative humidity created by the sample in a closed environment when in equilibrium. The procedure uses a water activity meter constructed by David Brookman & Associates (DB&A). The DB&A Water Activity Meter uses an Omega Engineering HX92C Relative Humidity indicator to measure the relative humidity within a closed environment containing the sample. The Omega probe converts the relative humidity (R.H.) into milliamperes (ma), where 4 ma equals 0% R.H. and 20 ma equals 100% R.H. The water activity meter is calibrated to

11.3% R.H. using a saturated solution of LiCl and to 75.3% R.H. using a saturated solution of NaCl.

The samples are manually macerated in a plastic bag and then transferred to a 30 ml sample bottle. The bottles are filled with sample to at least 1 cm from the shoulder. The bottles are capped until use and stored at room temperature. Measurements are taken by screwing the sample bottle onto the DB&A meter probe and the bottle probe assembly is maintained in a vertical position in a rack. Measurements are taken at hourly intervals at room temperature (20 – 22°C) until such time that successive readings do not vary more than 1%.

Random sampling of the jujubes was conducted. The water activity (a_w) was determined to be 0.507, 0.515 and 0.544. These values are well below levels those that favour the growth of microorganisms. It has been shown that microorganisms generally grow best between a_w values of 0.995 – 0.980 and most microbes will cease to grow at a_w values less than 0.900.

EXAMPLE 5: In vivo *Testing I*

The following example demonstrates the uptake of a functional ingredient (creatine) into the blood after consumption of a delivery system formulated with a matrix as described herein. Serum concentration levels of creatine of subjects who ingested either 3.5 gram of micronized creatine powder in capsule format or 3.5 gram of micronized creatine in jujubes (prepared as described in Example 2.5) were analysed by mass spectroscopy. Seven individuals were enrolled in the test, with an age range between 18 and 50 years. Individuals fasted overnight prior to administration of the creatine. The test protocol was as follows. Individuals were administered jujube containing 3.5g creatine with 8 oz water. Blood samples were taken every 15 minutes for the first hour, every 30 minutes for the second hour and subsequently at hourly intervals for a total of 8 hours after administration. After sufficient period of time to allow blood creatine levels to return to normal, the subjects were administered 5 capsules containing a total of 3.5g creatine with 8 oz water. Blood samples were taken at the same time intervals as indicated above. Results are shown in Figure 1.

The disclosure of all patents, publications, including published patent applications, and database entries referenced in this specification are specifically incorporated by reference in their entirety to the same extent as if each such individual patent, publication, and database entry were specifically and individually indicated to be incorporated by reference.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. An oral gel delivery system for antacids comprising one or more antacids substantially uniformly dispersed in a gel matrix, said delivery system having a final moisture content of between about 10% and about 40% by weight and a water activity of less than about 0.9, and said gel matrix comprising:
   a) one or more hydrocolloids;
   b) one or more sugars, sugar syrups, sugar alcohols, or a combination thereof; and
   c) one or more polyhydric alcohols.

2. The oral gel delivery system according to claim 1, wherein said delivery system has a final pH between about 6.0 and about 9.0.

3. The oral gel delivery system according to claim 1 or 2, wherein said one or more antacids comprises up to about 40% by weight of said delivery system.

4. The oral gel delivery system according to any one of claims 1, 2 or 3, wherein said delivery system comprises between about 0.1% and about 17% by weight of said one or more hydrocolloids, between about 15% and about 55% by weight of said one or more sugars, sugar syrups, sugar alcohols, or combination thereof, and between about 5% and about 50% by weight of said one or more polyhydric alcohols.

5. The oral gel delivery system according to any one of claims 1, 2, 3 or 4, wherein said one or more hydrocolloids are selected from the group of: gelatine, gellan, pectin, modified starch, cellulose and modified cellulose.

6. The oral gel delivery system according to any one of claims 1, 2, 3, 4 or 5, wherein said one or more sugars, sugar syrups or sugar alcohols are selected

from the group of: corn syrup, high fructose corn syrup, maltitol syrup and isomalt syrup.

7. The oral gel delivery system according to any one of claims 1, 2, 3, 4, 5 or 6, wherein one or more polyhydric alcohols are selected from the group of: glycerol, lower alkyl ester derivatives of glycerol, propylene glycol and short chain polyalkylene glycols.

8. The oral gel delivery system according to any one of claims 1, 2, 3, 4, 5, 6 or 7 further comprising one or more other functional ingredients, wherein the total amount of said one or more antacids and said one or more functional ingredients is less than or equal to 40% by weight of said delivery system.

9. The oral gel delivery system according to claim 8, wherein said one or more other functional ingredients are selected from the group of: antiflatulants, H_2 receptor antagonists, proton pump inhibitors, local anaesthetics, deglycyrrhizinated liquorice, rafting agents, carboxymethyl cellulose and activated charcoal.

10. An oral gel delivery system for antacids comprising one or more antacids substantially uniformly dispersed in a gel matrix, said delivery system having a final moisture content of between about 10% and about 30% by weight and a water activity of less than about 0.7, and said gel matrix comprising:
    a) one or more hydrocolloids selected from the group of: modified starch, gelatine, gellan, pectin, cellulose and modified cellulose;
    b) one or more sugar syrups selected from the group of: corn syrup, high fructose corn syrup, maltitol syrup and isomalt syrup, and
    c) one or more polyhydric alcohols selected from the group of: glycerol and propylene glycol.

11. The oral gel delivery system according to claim 10, wherein said delivery system has a final pH between about 6.0 and about 9.0.

12. The oral gel delivery system according to claim 10 or 11, wherein said one or more antacids comprises up to about 40% by weight of said delivery system.

13. The oral gel delivery system according to any one of claims 10, 11 or 12, wherein said delivery system comprises between about 0.1% and about 17% by weight of said one or more hydrocolloids, between about 15% and about 55% by weight of said one or more sugar syrups, and between about 5% and about 50% by weight of said one or more polyhydric alcohols.

14. The oral gel delivery system according to any one of claims 10, 11, 12 or 13 further comprising one or more other functional ingredients, wherein the total amount of said one or more antacids and said one or more functional ingredients is less than or equal to 40% by weight of said delivery system.

15. The oral gel delivery system according to claim 14, wherein said one or more other functional ingredients are selected from the group of: antiflatulants, H_2 receptor antagonists, proton pump inhibitors, local anaesthetics, deglycyrrhizinated liquorice, rafting agents, carboxymethyl cellulose and activated charcoal.

16. Use of a gel matrix comprising:
    a) one or more hydrocolloids;
    b) one or more sugars, sugar syrups, sugar alcohols, or a combination thereof, and
    c) one or more polyhydric alcohols,

in the preparation of an oral gel delivery system for antacids, wherein said delivery system comprises one or more antacids substantially uniformly dispersed in said gel matrix, and said delivery system has a final moisture content of between about 10% and about 40% by weight and a water activity of less than about 0.9.

17. The use according to claim 16, wherein said delivery system comprises up to about 40% by weight of said one or more antacids.

18. A process for preparing an oral gel delivery system for antacids, said process comprising the steps of:

(i) preparing a blend of one or more hydrocolloids, one or more sugars, sugar syrups, sugar alcohols, or a combination thereof, and optionally water at a temperature of less than 100°C, wherein said hydrocolloid(s), said sugars, sugar syrups and/or sugar alcohols and said water are in a ratio that will provide a final moisture content to the delivery system of between about 10% and about 40% by weight;

(ii) reducing the temperature of said blend to between about 50°C and about 80°C;

(iii) dispersing one or more antacids in a solvent comprising one or more polyhydric alcohols at a temperature at or below about 70°C to provide a solvent mixture;

(iv) combining said blend from step (ii) with said solvent mixture to provide a gel matrix, and

(v) moulding said gel matrix to provide said oral gel delivery system.

19. The process according to claim 18, wherein the amount of said one or more antacids dispersed in said solvent in step (iii) provides up to 40% by weight of said antacid(s) in the final delivery system.

20. The process according to claim 18 or 19, wherein preparing said blend in step (i) is at a temperature between about 60°C and about 80°C.

21. The process according to any one of claims 18, 19 or 20, wherein dispersing said one or more antacids in said solvent in step (iii) is at a temperature below about 50°C.

22. An oral gel delivery system for antacids prepared by the process of any one of claims 18, 19, 20 or 21.

23. Use of the oral gel delivery system according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 to deliver an effective amount of one or more antacids to an animal in need thereof.

24. The use according to claim 23, wherein said one or more antacids are for decreasing excess gastric acidity in said animal.

25. The use according to claim 23, wherein said one or more antacids are for alleviating symptoms associated with hyperacidity; acid indigestion; sour stomach; gastritis; heartburn; pyrosis; dyspepsia; gastritis; oesophagitis; gastroesophageal reflux; peptic ulcer or duodenal ulcer in said animal.

26. The use according to any one of claims 23, 24 or 25, wherein said animal is a human.

27. Use of the oral gel delivery system according to any one of claims 10, 11, 12, 13, 14 or 15 to deliver an effective amount of one or more antacids to an animal in need thereof.

28. The use according to claim 27, wherein said one or more antacids are for decreasing excess gastric acidity in said animal.

29. The use according to claim 27, wherein said one or more antacids are for alleviating symptoms associated with hyperacidity; acid indigestion; sour stomach; gastritis; heartburn; pyrosis; dyspepsia; gastritis; oesophagitis; gastroesophageal reflux; peptic ulcer or duodenal ulcer in said animal.

30. The use according to any one of claims 27, 28 or 29, wherein said animal is a human.

31. A kit for the delivery of antacids to an animal comprising one or more units of the oral gel delivery system according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 and optionally instructions for use.

32. A kit for the delivery of antacids to an animal comprising one or more units of the oral gel delivery system according to any one of claims 10, 11, 12, 13, 14 or 15 and optionally instructions for use.

33. The kit according to claim 31 or 32, wherein said animal is a human.

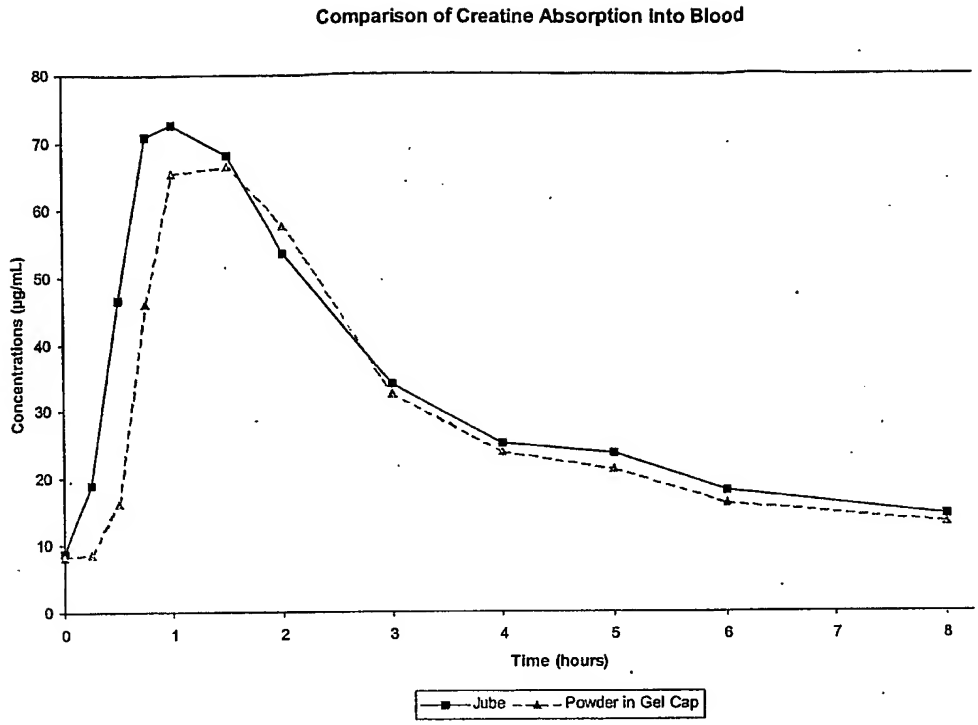

Comparison of Creatine Absorption Into Blood
Concentrations (µg/mL)
0
10
20
30
40
50
60
70
80
0
1
2
3
4
5
6
7
8
Time (hours)
Jube
Powder in Gel Cap

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/001896

A. CLASSIFICATION OF SUBJECT MATTER
A61K-9/00, A61K-9/14, A61K-31/00, A61k-9/127, A23L-1/29, A23L-1/00, A23G-3/00, G01F-1/56

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K, A23L, A23G, G01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, Delphion, Esp@cenet, USPTO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No(s).
Y	WO 03/088755 (Farber et al) October 30, 2003 (whole document)	1-33
X Y	WO 00/16743 (Chrstensen), March 30, 2000 (whole document)	1, 2, 4 -7, 10, 11, 13, 16 1- 33
Y	WO 03/026438 (Faber et al) April 03, 2003 (whole document)	1-33
Y	GB 691 782 (Baker et al) May 20, 1953 (whole document)	1-33
Y	WO 98/20860 (Bubnis et al) May 22, 1998 (whole document)	1-33
Y	WO 99/26491 (Yang et al) June 03, 1999 (whole document)	1-33

[ ] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 February 2005 (04-02-2005)	16 March 2005 (16-03-2005)
Name and mailing address of the ISA/CA *Canadian Intellectual Property Office* *Place du Portage I, C114 - 1st Floor, Box PCT* *50 Victoria Street* *Gatineau, Quebec K1A 0C9* Facsimile No: 001(819)953-2476	Authorized officer Geeta Chowdhury (819) 956-6129

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2004/001896

Patent Document Cited In Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO03088755	30-10-2003	EP1496751 A1	19-01-2005
		US2004237663 A1	02-12-2004
WO0016743	30-03-2000	AU744737 B2	28-02-2002
		AU6029499 A	10-04-2000
		CA2344678 A1	30-03-2000
		EP1115377 A1	18-07-2001
		US6387381 B2	14-05-2002
		WO0016743 A1	30-03-2000
WO9926491	03-06-1999	AT234022T T	15-03-2003
		AU736140 B2	26-07-2001
		AU775206 B2	22-07-2004
		AU1527399 A	15-06-1999
		AU8363101 A	10-01-2002
		BR9806990 A	14-03-2000
		CA2278369 A1	03-06-1999
		CN1098642C C	15-01-2003
		DE69812074D D1	17-04-2003
		DE69812074T T2	24-12-2003
		DK966208T T3	23-06-2003
		EP0966208 A1	29-12-1999
		EP1340428 A2	03-09-2003
		ES2194373T T3	16-11-2003
		PL334772 A1	13-03-2000
		PT966208T T	31-07-2003
		US6673380 B2	06-01-2004
		US2004137111 A1	15-07-2004
		WO9926491 A1	03-06-1999
WO9820860	22-05-1998	AU5105398 A	03-06-1998
		WO9820860 A2	22-05-1998
WO03026438	03-04-2003	US2004013732 A1	22-01-2004
		US2004052852 A1	18-03-2004
		WO03026438 A1	03-04-2003
		WO03026439 A1	03-04-2003
GB		NONE	